IN THE CIRCUIT COURT
OF MADISON COUNTY, TENNESSEE
FOR THE TWENTY-SIXTH JUDICIAL DISTRICT AT JACKSON

ROLF G.S. HAZLEHURST and ANGELA HAZLEHURST,
Plaintiffs,

vs.

E. CARLTON HAYS, M.D. and THE JACKSON CLINIC PROFESSIONAL ASSOCIATION,
Defendants.

NO. C-04-149 DIV II
JURY DEMANDED

AND

WILLIAM YATES HAZLEHURST, a minor by ROLF G.S. HAZLEHURST and ANGELA HAZLEHURST, As Natural Parents and Next Friends,
Plaintiffs,

vs.

E. CARLTON HAYS, M.D. and THE JACKSON CLINIC PROFESSIONAL ASSOCIATION,
Defendants.

NO. C-10-290 DIV II
JURY DEMANDED

VIDEO DEPOSITION OF

ANDREW W. ZIMMERMAN, M.D.

ORIGINAL

VIDEO DEPOSITION of ANDREW W. ZIMMERMAN, M.D. taken at the request of the Defendants pursuant to applicable rules of the Tennessee Rules of Civil Procedure before Star Gates Curry, a notary public in and for the Commonwealth of Massachusetts, on November 9, 2016 commencing at 9:03 a.m. at the University of Massachusetts Medical Center, 55 Lake Avenue, Worcester, Massachusetts.

A P P E A R A N C E S:

FOR THE PLAINTIFF:

W. BRYAN SMITH, ESQ.
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FOR THE DEFENDANT:

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I N D E X

DEPONENT: ANDREW W. ZIMMERMAN, M.D.

EXHIBITS

PROCEEDINGS

THE VIDEOGRAPHER: This is the videotape deposition of Dr. Andrew Zimmerman taken by the defendants in the matter of Rolf G. S. Hazlehurst and others versus E. Carlton Hays, M.D. and others, pending in the Circuit Court of Madison County, Tennessee for the Twenty-Sixth Judicial Circuit at Jackson, being held today, November 9th, 2016, in the offices of Dr. Zimmerman at UMass Medical Center, 55 Lake Avenue, Worcester, Massachusetts, commencing at 9:03 a.m.

The court reporter's name is Star Gates Curry, she is from the firm of McCarthy Reporting Service, 12 Harvard Street, Worcester, Massachusetts.

I am the videotape specialist. My name is Sean McDonald and I represent McCarthy Reporting Service of Worcester, Massachusetts.

Counselors, if you would introduce yourselves please.

MR. SMITH: Bryan Smith for Yates Hazlehurst.

MR. PHILLIPS: Marty Phillips for Dr.

Hays and the Jackson Clinic.

ANDREW ZIMMERMAN, M.D.,

having been satisfactorily identified by the production of his Federal- or State-issued photo identification, and duly sworn by the Notary Public, was examined and testified as follows:

EXAMINATION BY MR. PHILLIPS:

Q. Would you tell us your name please, sir.

A. Andrew Zimmerman.

Q. Dr. Zimmerman, we met a moment ago. I'm Marty Phillips and in this case I represent Dr. Carlton Hays and the Jackson Clinic. You've been identified as an expert on behalf of the plaintiff in this case. Do you understand that?

A. Yes.

Q. And you know my purpose for being here is to take what's called your discovery deposition, that is to find out the opinions you hold and the bases for them. You understand that, right?

A. Yes.

Q. And this is not the first occasion that you've been called upon to come to a deposition and articulate your opinions, is it?

A. Correct.

Q. So you understand how this process works?

A. Yes, I do.

Q. All right.

MR. PHILLIPS: Just for the record at this point, let's note that this is a deposition being taken of an expert disclosed pursuant to Rule 26, it's taken pursuant to the Tennessee Rules of Civil Procedure and it is a discovery deposition.

MR. SMITH: That's right. Dr. Zimmerman will read and sign. The only qualification I would make is that Dr. Zimmerman is also a -- we consider him to be a treating physician. I know you have a -- you're saying Rule 26, but I'm not agreeing that he is necessarily a Rule 26, but he is being taken pursuant to the Rules of Tennessee Civil Procedure as an expert witness per the order that

the judge issued.

MR. PHILLIPS: We agree that this is a discovery deposition?

MR. SMITH: Yes, yes. That's what I'm saying.

MR. PHILLIPS: Yes.

MR. SMITH: In a roundabout way.

MR. PHILLIPS: Okay, good.

Q. Dr. Zimmerman, if during the course of the deposition you do not understand a question that I ask, please stop me and tell me that you don't understand my question. Okay?

A. Yes.

Q. I'll tell you at the outset I'm perfectly capable of asking a bad question. And I'll need your help to be sure that we're communicating, okay?

A. Yes.

Q. We're in a small room and so hopefully this won't be a problem, but should you have any difficulty hearing me, if you'd let me know I'll be glad to repeat my question. All right, sir?

A. Thank you.

Q. Yes, sir. As succinctly as you can

tell me, describe for me the opinions that you hold in this case.

A. My opinion is that -- that the Yates child -- Yates Hazlehurst had a regressive onset of autism following administration of vaccines and at the same time he had an ear infection, both of which -- both factors created inflammation and within 12 to 14 days after the immunization he began regressing.

We -- I saw Yates some years later in Baltimore County Krieger Institute and did some testing to look for signs of mitochondrial dysfunction. And these were later evaluated by Dr. Richard Kelley.

And subsequently I did not see Yates for follow-up but learned later that he was found to have a mitochondrial disorder. And it is my opinion that it is the underlying mitochondrial disorder that created the susceptibility factor in Yates that led to his autistic regression and change in brain function. And it is because of the mitochondrial -- underlying mitochondrial problem that Yates suffered this change in his brain function.

Q. Does that encapsulate your opinion in this case?

A. Yes.

Q. Okay. When you make a reference to the administration of vaccines, is there a particular time you're talking about? Or are you just talking about in general in Yates's situation?

A. He had an initial vaccine reaction at six months of age, but as far as I can tell he recovered from that. But then the second administration at I believe 11 months of age was the precipitating event.

Q. Could that have been on February the 8th, 2001?

A. I don't recall the exact date, but I would go with it.

Q. But it were -- it was the administration of vaccines right around his first birthday that you're making reference to if I understand correctly?

A. Correct.

Q. In your opinion were there any vaccines that were involved here, in your

opinion, other than the ones given around his first birthday? Which I'll submit to you the date is February 8th, 2001.

A. Could you repeat that?

Q. Yes, sir. You described for me your opinion that he had a regressive onset of autism following the administration of vaccines.

A. Correct.

Q. And in your opinion that occurred only after the February 8, 2001 administration of vaccines; is that right?

A. Yes.

Q. Assuming that those are the ones given around the one-year mark?

A. Correct.

Q. Okay. So we don't have anything to discuss with regard to vaccines given before that date or after that date in your opinion?

A. Well, the fact that he had a significant vaccine reaction previously is important because it was a -- an event that may have raised suspicions that he could have had -- would have been subject to another vaccine reaction.

Q. Is there a particular vaccine that was given on February 8th, 2001 that in your opinion is at issue here?

A. Commonly the MMR vaccine is attributed to inflammatory response, for merc inflammatory response, about ten days following immunization. But I have no opinion as to whether it was MMR or any other vaccine.

Q. Do you have any opinion about what component of any particular vaccine was involved here?

A. No.

Q. When you say that there was a vaccine reaction at about six months, what's the basis of that opinion?

A. From the -- reading the record that was my understanding that he had extreme irritability following that.

Q. Is that based upon information that the parents gave you or something you read in the medical record?

A. I believe it was both. But I'd have to -- I'd have to review that.

Q. Do you have the medical record

accessible to you?

A. I do. It's in a thumb drive.

Q. Okay. Are you able to look at it as we sit here now?

A. I don't have my laptop.

MR. PHILLIPS: Do you have a copy of that, Bryan, I can show him?

MR. SMITH: Yeah, I can pull it up. Not unless they get me on the Internet. Unless I can pull it up on my phone.

Q. While Mr. Smith is looking for that, let's continue talking.

Are there causes for fussiness and irritability in a child that's six months or so old other than a vaccine reaction?

A. Of course.

Q. Tell me the other things that could explain fussiness and irritability besides a vaccine reaction.

A. Constipation, diarrhea, any number of illnesses.

Q. Can you give me any other examples?

A. Cough, cold, hunger. But I think the -- the types of vaccine reactions, there are

many, many factors in vaccine reaction, but this was described as inconsolable crying which is something that I've seen over the years in -- in response to vaccines.

Q. But it could, of course, be in response to other things too, right?

MR. SMITH: Object to form.

A. Yes, it could.

Q. Okay. Has there been research done on whether vaccines cause autism?

A. A number of studies have been done to look at that. Epidemiological studies.

Q. And what conclusions have those studies reached?

A. The conclusions that have -- are that vaccines do not cause autism, that is there is no, no evidence, no direct evidence that they do, although the possibility of vaccine re -- vaccines causing autism in individual cases has not been ruled out.

Q. Tell me some of the studies that you're familiar with that stand for the proposition that vaccines do not cause autism.

A. Um, the --

MR. SMITH: Object to the form. That mischaracterizes his testimony, but go ahead.

A. The most famous one was Taylor in Great Britain, and after -- he did one of the first studies after Dr. Wakefield published his work. And that was the most impressive. And there have been others.

Q. Has the American Academy of Pediatrics taken a position on that topic?

A. Of course.

Q. And what does the American Academy of Pediatrics say about whether vaccines cause autism?

A. They say there is no direct evidence, epidemiological evidence, that vaccines cause autism.

Q. And are you a member of the American Academy of Pediatrics?

A. I am.

Q. How about the Center for Disease Control, what position does it take regarding whether vaccines cause autism?

A. Similar.

Q. Its position is vaccines do not cause

autism?

MR. SMITH: Object to the form.

A. Correct.

Q. And both of those organizations are well-respected, aren't they?

A. Of course.

Q. And they do sound research and reach conclusions that are scientifically valid and sound in your judgment?

A. Based on epidemiological studies in the past, but I think we are in a new era when a lot of research is being done now that helps us to understand the underlying metabolic basis of autism and I think this is going to change our approach to this problem.

Q. But that hasn't happened yet, has it?

A. It is happening now. And it is being published.

Q. But it hasn't been concluded yet?

A. It hasn't reached the epidemiological level at this point. We are in the midst of active research in this area and this is -- I don't expect that it's going to change the overall picture of immunizations but I expect

that it is going to change the way we approach the problem.

Q. Meaning what?

A. Once we have the biomarkers for the patients who have susceptibility to regression following immunizations, it will change our approach to -- to treatment of the children, to identify the children who are at risk.

Q. So in your opinion looking forward is, what you contemplate will happen, the change you see is in treatment of autistic children?

A. I think it will change the treatment but more importantly I think it will prevent the development of autism in quite a few children. Currently about 30 percent of children with autism undergo regression and we would like very much to understand the metabolic basis for that and how we can prevent it.

Q. Is it true that in about 90 percent of patients the cause of autism is unknown?

A. We're now up to, depending on whom you read, 30 to 40 percent can be identified genetically as to the causation. And some of these include mitochondrial disorders.

Q. So that would mean the majority of patients the cause of autism is unknown?

A. Still unknown, yes. But I should add, changing rapidly.

Q. Other than the American Academy of Pediatrics, the Center for Disease Control, what other organizations have taken a position on this issue about whether vaccines are associated with autism?

A. I don't know. I would imagine the AMA has something.

Q. The American Medical Association?

A. Yes.

Q. Are you a member of that organization?

A. I am.

Q. How about the Institutes of Medicine, have they taken a position?

A. Yes, they have.

Q. What's their position?

A. It's the -- it's the same. That there is no evidence for an association.

Q. Between vaccines and autism?

A. Right. No epidemiological evidence. That is looking at large groups of children.

Q. You at times serve as a reviewer for various publications, don't you?

A. Yes, I do.

Q. When you do that, what's involved and what's your job as a reviewer?

A. To be as critical, reasonably critical, as possible.

Q. Is it to evaluate the validity of the research that's been done?

A. Of course.

Q. And to be sure it's scientifically valid?

A. Of course.

Q. And is it also to assess the conclusion that is being reached based upon that research and investigation?

A. Yes.

Q. And to be sure that conclusion is scientifically valid?

A. Of course.

Q. You actually were a reviewer on the Immunization Safety Review done by the Institute of Medicine, weren't you?

A. I was.

Q. And in that document on which you're listed as a reviewer, the conclusion was that there is no association between vaccines and autism, correct?

A. As I recall, yes.

Q. Let me show you a copy here.

MR. PHILLIPS: And I'll be happy to substitute a copy, Bryan, since I didn't bring clean ones. But just so he can identify this document.

MR. SMITH: I would like to look at it too.

MR. PHILLIPS: I'm going to.

MR. SMITH: Okay.

(Handing document to witness.)

A. Yes, I --

Q. That is --

A. This is -- the year that was '04, right.

Q. And are you listed here as a reviewer?

A. Yes.

Q. And what's the page on which you're listed as a reviewer?

A. 8.

Q. Okay.

MR. PHILLIPS: I want to mark a clean copy of this as an exhibit and I'll supply that later. That will be Exhibit 1.

(Deposition Exhibit No. 1 marked.)

Q. Let's look at the conclusion reached here, see if this refreshes your recollection. Look at the first paragraph, what's that page number here?

A. 32. Oh, page 1, 32.

Q. All right. And look at that paragraph and see if that helps you refresh your recollection on the conclusion reached by the Institutes of Medicine for which you were a reviewer.

A. Yes, I agree with that.

Q. Tell me what it says.

A. It says there is no relationship, they see no relationship to vaccines, specifically MMR and thimerosal-containing vaccines, are causally associated with autism.

Q. And you agree with that statement?

A. In 2004 I do.

Q. Okay. Has there been anything published to change that position by the Institutes of Medicine?

A. Not by the Institute of Medicine, no.

Q. Okay.

A. And I -- I should add that I still to this day feel strongly that immunizations are important and I encourage my patients, even patients who feel they have been harmed and caused regression in their children, I still advocate vaccinations.

Q. Do you advocate vaccinations in children who have mitochondrial disorder?

A. Yes, under, I do, conditions.

Q. Is this information in the Institute of Medicine study that we've marked as Exhibit 1, is the conclusion and the information in here reliable and scientifically valid?

A. Yes.

Q. And you consider the publications by the Institutes of Medicine, particularly the Immunization Safety Review which we've marked as Exhibit 1, as a reliable authority?

A. At the time it was published, yes.

Q. Tell me if you can identify this page, Doctor.

(Handing document to witness.)

A. This is from the American Academy of Pediatrics on vaccine safety.

Q. And is that the information you were referring to earlier when you commented on the position of the American Academy of Pediatrics on whether vaccines cause autism?

A. Yes.

Q. And is that a reliable authority in your opinion?

A. Yes. I'm a member of the academy.

Q. It's what your professional organization has said, right?

A. Right.

Q. And in part this document, which we're going to mark as Exhibit 2, says, and I'll let you read along with me, "Over the past decade, questions have been raised regarding a relationship between autism and vaccines."

And then down in the next paragraph it says, "Research has been conducted on all these topics, and the studies continue to find vaccines

to be a safe and effective way to prevent serious diseases."

Did I read these two sections correctly?

A. Yes.

Q. And then it says here, "These studies do not show any link between autism and MMR vaccines, thi --

A. Thimerosal.

Q. -- thimerosal, multiple vaccines given at once, fevers or seizures."

Did I read that correctly?

A. Yes.

Q. And you agree with that, right?

A. Yes, with the exception that these are epidemiological studies and do not incorporate our new knowledge at this point.

(Deposition Exhibit No. 2 marked.)

Q. Are you familiar with the Cleveland Clinic?

A. Yes.

Q. What is its reputation in the medical field?

A. It's a good reputation.

Q. Are you familiar with its position on vaccines and autism?

A. I have not read that specifically, no.

Q. And are you familiar with its position about mitochondrial disorder?

A. Not exactly, no.

Q. Okay. Can you identify this document I've given you?

(Handing document to witness.)

A. This is Myths and Facts about Mitochondrial Diseases from Cleveland Clinic.

Q. And particularly on the second page of what we're going to mark as Exhibit 3, it says Myth, you see that?

A. Yes.

Q. And then it says immunization can be harmful to children with mitochondrial diseases, that's listed as a myth, isn't it?

A. Yes, it is.

Q. And then Fact, it says there is what?

A. "No clear evidence that immunizations themselves hurt patients with mitochondrial or metabolic disorders."

Q. Do you agree with those statements from this Cleveland Clinic document?

A. No, I do not. And I'm pretty sure I know the resource.

COURT REPORTER: Pretty sure what?

THE WITNESS: I know the resource.

(Deposition Exhibit No. 3 marked.)

Q. You know Dr. Richard Kelley, you mentioned him earlier?

A. Yes, of course.

Q. Here's an article that was marked in his deposition but I'll show you the first page of it. Can you identify this document for the record please?

(Handing document to witness.)

A. This is Weissman et al and in 2008.

Q. And Dr. Kelley is one of the authors of that article?

A. Correct.

Q. Where is it published?

A. PLoS One.

Q. Is that a reliable authority in your opinion?

A. Yes.

MR. PHILLIPS: I'm going to mark a copy of this article as Exhibit 4.

(Deposition Exhibit No. 4 marked.)

Q. I'm going to show you a particular section of this article, Doctor. Are you able to see this okay here? What page are we on?

A. Page 4.

Q. All right. Read where it's highlighted here.

A. "Recently" --

Q. And we're reading under the discussion section one, two -- third paragraph down, right?

A. Correct.

Q. Okay, go ahead.

A. (Reading) Recently, there has been increased concern regarding a possible causative role of vaccines in autistic children with an underlying mitochondrial cytopathy. For one of our 25 patients, the child's autism deterioration appeared to follow vaccination. Although there may have been a temporal relationship with the events in this case, such timing has been a

temporal relationship of the events in -- such timing does not prove causation. That said, there might be no difference between the inflammatory or catabolic stress of vaccinations and that of common childhood diseases, which are known precipitants of mitochondrial regression. Large, population-based studies will be needed to identify a possible relationship of vaccines with autistic regression in persons with mitochondrial cytopathy.

Q. Do you agree with that statement?

A. Yes and no. I think they were -- they were being politically correct and wanted to avoid controversy because I'm sure -- I have the opinion myself and others currently working in this field believe there is a reason for a regression, probably different reasons in different children who regress and develop autism. But I think that the time will come before very long when we understand this, have biomarkers and we can approach this not through -- not first through large epidemiological studies, but rather through studying directly the children who are affected

compared to other children with autism who are not. And this is -- this is coming very soon. And it's actually going on now.

Q. So the passage that we read from the Dr. Kelley article that we've marked as Exhibit 4 concluded with the statement saying large, population-based studies will be needed to identify a possible relationship of vaccination with autistic regression in persons with mitochondrial cytopathies. Have those large, population-based studies been done to your knowledge?

A. No.

Q. Dr. Kelley provided a I'm going to call it a handout, he probably would call it something else, that he said he gave to physicians and maybe to patients. And I want to show you that document and see if you've ever seen that before.

A. Yes, of course I have.

Q. And what's the title at the top?

A. Evaluation and Treatment of Patients with Autism and Mitochondrial Disease.

Q. Okay. And it indicates at the bottom

when it was prepared?

A. June 13th, 2009.

Q. And it says "this summary" -- read the highlighted sentence.

A. "This summary reflects the clinical experience with a single institution's autism population and diagnostic laboratories and, therefore, may differ substantially from experience elsewhere."

Q. Okay. In the document, and you said you're familiar with it, on page 12 of the document, and let me put this so we can read along together.

Would you read what's highlighted here in orange?

A. (Reading) The currently used acellular pertussis vaccine DTaP appears to be safe and, in our experience, has not been associated with autistic regression. We believe it is much better to immunize with DTaP than risk infection with highly inflammatory and potentially damaging community-acquired pertussis. Um, while we have not seen regression in AMD in recent years clearly associated with time -- in time with the

standard immunizations given in the first year, the MMR vaccine has been temporally associated, if rarely, with regressions -- with regression in AMD and other mitochondrial diseases when given in the second year. Doubtless some of these regressions are coincidental, since the usual age for giving the MMR falls within the typical window of vulnerability for AMD regression.

Q. Do you agree with that statement?

A. Yes.

Q. So in your experience you have not seen any association between regression and an MMR vaccine given within the first year?

A. I have. In my own experience.

Q. This handout that Dr. Kelley put together that you reviewed states that there had not been observed an association between any regression and an MMR given at one year, correct?

A. That's what it says, but I didn't write that.

Q. Yes, sir. But he's describing the experience in this paper at Kennedy Krieger Institute, right?

A. Right.

Q. And you were part of that at the time you read the paper?

A. I had nothing to do with writing this, this is Richard Kelley's own.

Q. Okay.

A. I'm not involved with this.

Q. Did you review it beforehand and approve it?

A. No.

Q. Did you suggest any changes to it?

A. No.

Q. Okay.

A. I learned from Richard Kelley, I believe I -- he may have learned some things from me. But we were independent practitioners. He's much more of a laboratory-based person than I am. But he has his -- he has his own writing there.

Q. I didn't tell you this when we started, but during the course of the deposition if you need a break, I'll be happy to accommodate you, so you just let me know.

A. I can't get by there.

Q. I'll make a way for you to get out.

Do you have any affiliation with an

organization Autism Speaks?

A. I do.

Q. What is that affiliation?

A. Um, I have been on -- I've been involved with them, I've never been funded by them, but I have -- I was involved with them from the -- from the start before they were Autism Speaks. I was involved with an organization called Cure Autism Now that melded with Autism Speaks.

Q. Have you been involved with any other autism organizations?

A. The Autism Research Institute, ARI.

Q. Are you familiar with the position of Autism Speaks on vaccines and autism?

A. Yes, I am.

Q. What is their position?

A. Similar to the Academy of Pediatrics.

Q. And can you identify this as a statement by Autism Speaks concerning vaccines and autism?

(Handing document to witness.)

A. Yes.

Q. What does it say?

A. That vaccines do not cause autism.

MR. PHILLIPS: Let's mark that as Exhibit 5.

(Deposition Exhibit No. 5 marked.)

Q. What is the Johns Hopkins newsletter?

A. A newsletter from Johns Hopkins.

Q. How is it prepared?

A. By the Hopkins people.

Q. I'm sorry?

A. By people at Hopkins.

Q. And so if a particular statement is made or a particular position is taken, how is that done?

A. Well, it's usually a consensus among people on the faculty.

Q. You okay?

A. I'm fine.

Q. Need some water or something?

A. I have coffee, that's better.

Q. Okay, all right.

And how long were you on the faculty at Johns Hopkins?

A. I'm still on the faculty at Johns

Hopkins.

Q. When did that association begin?

A. Well, I trained there in '74 to '77, and went back to Kennedy Krieger and Hopkins in '94. I left in 2010 to move to Massachusetts. But I'm still on the faculty both at Kennedy Krieger and at Hopkins.

Q. So even when you left in 2010 I think you said you maintained your affiliation with John -- Johns Hopkins?

A. Correct.

(Deposition Exhibit No. 6 marked.)

Q. Let's look at this Johns Hopkins newsletter. What's the date on it?

A. March 31st, 2016.

Q. What's the title of the Johns Hopkins newsletter?

A. Debunking Common Myths about Autism.

Q. And if we turn to page 2, there is a paragraph that says Myth, you see that?

A. Mm-hmm.

Q. Yes?

A. Yes.

Q. And it says the myth is early childhood vaccinations can sometimes lead to autism. That's listed as a myth, right?

A. Mm-hmm.

Q. Yes?

A. Yes.

Q. And then it states the fact in this Johns Hopkins newsletter, "The myth was circulated by a fraudulent 1998 article in Lancet in which British gastroenterologist Andrew Wakefield claimed to have found a link between autism and the measles, mumps and rubella (MMR) vaccine. The article has since been retracted, and Wakefield has been condemned by the scientific community for manipulating evidence. Yet the effects of Wakefield's article were widespread: Following his 1998 claim, vaccination rates in Ireland and England fell sharply, leading to an almost 20-fold increase in reported cases of measles from 1998 to 2007."

Did I read that correctly?

A. Yes.

Q. And then it continues by saying "many people still believe in this myth," and it's

referring to the myth that early childhood vaccinations can sometimes lead to autism, right?

A. Correct.

Q. And then it says, "but nothing could be further from the truth. We have a highly convincing body of evidence showing that there is no correlation between vaccines and autism. A 2013 study conducted by the Center for Disease Control (CDC) found no significant correlation between antibody stimulating proteins (such as those found in vaccines) and autism. A total of nine CDC-funded studies have shown that popular vaccine ingredients, such as mercury-based thimerosal, which were once thought to lead to autism, have been reported to have no correlation with autism."

Did I read that correctly?

A. Yes.

Q. And that's in the Johns Hopkins newsletter dated March 31, 2016?

A. Correct.

Q. Do you agree with those statements?

A. Not entirely. I do think that -- that there was much information -- misinformation

brought about by Dr. Wakefield and it's -- this has set the field back. I think that -- that we -- we have worked very hard to try to reassure the public and I agree with doing that because I am very supportive of vaccinations, immunizations in general.

But at the same time, I take care of a lot of patients with autism. And I -- and I work very hard every day that I see patients to debunk this myth and to reassure families that vaccinations are good because, as you probably know, there are many parents out there who refuse to immunize their children because, especially after their child has regressed following vaccines, and I've tried my best to reassure them that vaccines do not directly cause autism.

Q. And that --

A. I do not convince very many to do so. In fact, I just dealt with this two days ago at great length.

But we are now in the midst of -- of some exciting research being done in Arkansas and elsewhere, Dr. Frye and Dr. Shannon Rose, Dr. Joe James, and others in other places, and we

ourselves are conducting some research in mitochondrial functions that I think will help us to understand a relationship, probably most likely an uncommon relationship, but it does exist and it does not -- it is not evident in the studies that have been done to date.

Q. Are you aware of any study, any published study, that exists today that would disagree with all these studies that we've been talking about thus far that would say there is an association or there is a causal link between vaccines and autism?

A. Not directly, no. But the difference is the mitochondrial piece. And I think that has not been taken into consideration and will be very soon.

Q. I understand your opinion about that looking in the future. But I'm interested in knowing as we sit here today there is not any published study that you're aware of that would tell us that there is a causal link between vaccines and autism; am I right?

A. Correct.

Q. Okay. And you provided a number of

articles to Mr. Smith which he provided to me in this case that you at least communicated through him were some that you intended to rely upon for your opinions in this case, right?

A. Right.

Q. But none of them say that vaccines cause autism, do they?

A. No.

Q. Even in mitochondrial-disordered children?

A. I don't know if I provided the Poling article but that was -- that was one case in which there was an association that was published.

Q. Other than that possible exception, which is not really a broad-based study but just one case issue, there is not anything that you've provided that would indicate a link between vaccines and autism even in children with mitochondrial disorder, true?

A. True. I did provide articles that show the work that is going on in mitochondrial disorders.

Q. So if I understand correctly, we have

maybe two different things at play here in your opinion. We have the scientific data and research as it currently exists, and then we have the research as may be developed in the future?

A. That is going on now.

Q. Yes.

A. Yes.

Q. And you're not aware of any research or study that has been completed as of now and published that says vaccines cause autism?

A. Correct.

Q. Is there some association between the Institute for Vaccine Safety and Johns Hopkins?

A. Is that Neal Halsey?

Q. Well, let me show you this document. You'll see that it makes a reference both to the Institute of Vaccine Safety and Johns Hopkins and I was wondering if you could tell me how, if at all, those organizations are connected?

A. I think the Institute for Vaccine Safety is at Hopkins as I recall, yeah. Yeah. And it's run by Neal Halsey, who is an infectious disease expert. Yeah, here it is.

Q. Is that document you hold in your hand

something that's been published by the Institute for Vaccine Safety in affiliation with Johns Hopkins?

A. Yes.

Q. And you're familiar with that?

A. I'm familiar with Neal Halsey, yeah.

Q. Is that a reliable authority in your opinion?

A. Of course.

MR. PHILLIPS: Let's -- let's mark that as Exhibit 7.

(Deposition Exhibit No. 7 marked.)

Q. What does Exhibit 7 say about any association between vaccines and autism from Johns Hopkins and the Institute for Vaccine Safety?

A. They say there is no association.

Q. And here's another publication that it references both the Institute for Vaccine Safety and Johns Hopkins. Can you identify that for us?

(Handing document to witness.)

A. It's about thimerosal in vaccines showing no relationship.

Q. Are you familiar with this publication from Johns Hopkins and the Institute for Vaccine Safety?

A. Not this specific one, but I'm familiar with the institute and Dr. Halsey.

Q. Is this information in this document a reliable authority in your opinion?

A. Yes. Given the current ev -- published evidence, yes.

MR. PHILLIPS: We'll mark that as Exhibit 8.

(Deposition Exhibit No. 8 marked.)

Q. In your opinion has any suggested connection between thimerosal and autism been conclusively disproven?

A. In my mind thimerosal does not cause autism, no.

Q. Okay. So you think that theory has been debunked?

A. Yes.

Q. You talked earlier about Dr. Wakefield and we made some reference to him, even reading from the Johns Hopkins newsletter. But do you

agree that his publication in The Lancet in 1998 was really responsible for starting this concern that vaccines cause autism?

A. As I said, I think it diverted our attention from studying the real problems.

Q. He was kind of the father of this theory, wasn't he?

A. He had his own idea that -- about MMR, yes.

Q. And ultimately that article was retracted, correct?

A. Correct.

Q. And his research was proven to be fraudulent; is that true?

A. I'm not sure -- I'm not sure I would characterize it as research.

Q. Okay.

A. I think that's generous.

Q. Okay. His shall we say his alleged data was proven to be fraudulent?

A. Yes.

Q. Would that be an accurate description?

A. Yes.

Q. Are you familiar with the work of Dr.

Geier?

A. Yes, I am. Very familiar.

Q. And tell me your position on that.

A. I'm -- I'm not fond of his work.

Q. What did he conclude?

A. Well, he -- he was very focused on the male hormones in autism. And -- but he also had a belief that there was a relationship to vaccines.

Q. And his theory was disproven too, right?

A. Well, I think -- yes, Dr. Geier had not much basis for what he -- what he hypothesized.

Q. In your -- in your opinion whatever opinions he voiced on the issue were not scientifically valid, true?

A. True.

Q. Part of what Exhibit 8 says, this Johns Hopkins document in conjunction with the Institute for Vaccine Safety, is that the MMR vaccination is not associated with an increased risk of pervasive developmental disorders, right?

A. Yes. That's an older term for autism

spectrum disorder.

Q. And then it says, "We found no convincing evidence that MMR vaccination increases the risk of autism or other PPDs." Is that what it says?

A. Yes.

Q. And then it references in particular Dr. Halsey and says that vaccines do not cause autism, correct?

A. Correct.

Q. And this document is dated October 28, 2016?

A. That's when it was downloaded. I don't know what the original date was.

Q. Okay.

A. I would imagine that the date was much earlier because nobody refers to PDDs anymore.

Q. You made a reference earlier to potential detriment, and correct me if I'm getting the words wrong, but you basically made a comment about potential harm or detriment to an idea that vaccines cause autism, right?

A. Yes.

Q. And what's the harm? What's the

detriment?

A. Well, when the public loses faith in vaccines you hurt immunity and that -- that is harmful, potentially harmful to the child who is not immunized as well as to other children.

Q. So you I think told us that you recommend vaccination of your patients with mitochondrial disorder, right?

A. Yes. Under ideal circumstances.

Q. And do you recommend vaccinations in your children and your patients who have had -- thought to have had a reaction to a vaccine?

A. I do. But, again, they should be given under CDC guidelines for immunizations. The child should not be ill, should not have fever, should have no associated illnesses at the time they're vaccinated.

Q. Do you --

A. And if the child has a known form of mitochondrial dysfunction, not only should they be free of immunization -- free of infections, we can recommend something to prevent inflammation.

Q. You were an expert witness on behalf

of the government in the Cedillo case, weren't you?

A. Yes, I was. Or was about to be.

Q. You wrote a report for submission in that case?

A. Yes, I did.

Q. Okay. Can you identify this as a copy of your report from the Cedillo case?

(Deposition Exhibit No. 9 marked.)

(Handing document to witness.)

A. Yes, it is.

Q. Okay. And it is dated April 24th, 2007?

A. Yes.

Q. Do you recall that one of the experts for the Cedillo -- excuse me, one of the experts for the Cedillo family was Dr. Krigsman?

A. Yes, yes.

Q. And you disagreed with Dr. Krigman -- Dr. Krigsman's conclusions in that case, didn't you?

A. I'd have to review what they were but he -- he's a gastroenterologist and -- but I'd

have to review what he said.

Q. Is -- the information in this report, which we're going to mark as Exhibit 9, was obviously accurate and scientifically valid when you drafted the report, correct?

A. Correct. But I should add at the very same time that report, I drafted that report, we were publishing the Poling case. And the reason I believe that I was not called to testify in the Cedillo case was that I told them I think there are rare exceptions, like Poling, and therefore I was not asked to testify.

Q. Is autism primarily a genetically determined disorder?

A. Primarily, but --

Q. And what does that mean, that autism is primarily a genetically determined disorder?

A. That the -- that it's heritable, that the genes, there are genes involved either directly or indirectly.

Q. From a layperson's standpoint would that be tantamount to saying that one is born with it?

A. Not necessarily. One has a

predisposition to it. I think that the -- two siblings, two identical twin siblings, can have, one can have autism and the other doesn't, or they have different degrees of it. So there are modifying factors beyond the genes, we call these epigenetic.

Q. You make a statement here that says: There is strong evidence that the origins of autism begin before birth, based upon genetic and anatomical studies as well as clinical findings at birth in children who go on to develop autism.

A. True. But at the same time there are modifying factors.

Q. And then you describe autism and use this phrase, "the appearance of pre-programmed disordered expression of genes and pre-existing cellular abnormalities that result in the child's regression with loss of language and social skills."

A. Yes.

Q. You write in this report, "There is no scientific basis for a connection between measles, mumps and rubella (MMR) vaccine or mercury intoxication and autism." True?

A. True at the time. Under the circumstances.

Q. "Despite well-intentioned and thoughtful hypotheses and widespread beliefs about apparent connections with autism and regression, there is no sound evidence to support a causative relationship with exposure to both, or either, MMR and/or mercury."

A. At the time that was my thinking.

Q. You make another statement, "Again, there is no scientific basis for attributing autism to MMR administration."

You make that statement, right?

A. Yes.

Q. Is it true that autism in most cases begins before birth and the maternal environment in the womb is likely to be important in the process?

A. There is no doubt about that. I think that the maternal environment may include maternal antibodies which is probably another cause for autism.

COURT REPORTER: What's that?

A. Which is another cause for autism.

And it is not genetic in the usual sense so it doesn't have to be genetic. It can be genetic in the mother's susceptibility to develop antibodies to the fetal brain that then affect her child.

This is another active area of research that I was involved with at the start and now is conducted by Dr. Judy Vanderwater and Paul Ashwood at UC Davis. And this is going to be another major cause for autism.

So our knowledge in this field is expanding rapidly. And what we saw a few years ago is now out of date. At least in terms of research that's going on.

Q. Is autism a disease of cell death or brain development?

A. It's both. There is -- there are alterations in cells but it's -- it's primarily development.

Q. Give me some understanding in general about the number of autism patients who have regression who do not have mitochondrial disorder.

A. We don't know because it hasn't been studied.

Q. Would it be true that there are autism patients who have regression but do not have underlying mitochondrial disease?

MR. SMITH: Object to the form.

A. Most certainly.

Q. Would it be true that there are patients who have autism and a mitochondrial disorder but do not have regression?

A. I would imagine there are but we don't know.

Q. Do you consider yourself an expert in mitochondrial disorder?

A. No. I'm a -- primarily a clinician with a great interest in -- in the metabolic basis and genetic basis of autism and other developmental disorders. But I'm not a laboratory person directly. I collaborate with people like Richard Kelley and others.

Q. Are you arguing in this case for some link between vaccines and autism?

A. Not in general, no. I'm, as I said, I'm -- I believe there are exceptional cases that are going to be difficult, have been difficult to ferret out the reasons for them, and I'm -- I'm

hoping to see the day when we understand the relationships between the metabolic basis and whatever it is, whether it's vaccines. I'm not -- I'm not interested in arguing about vaccines and certainly not until we understand all the causes, but I think there are exceptional cases and I know that from the Poling case and other patients I've seen, but haven't published.

Q. You're not aware of any theory espousing a relationship between vaccines and regression having been tested, are you?

A. A theory? No.

Q. Yeah, the argument that there might be some association between vaccines and regression, that's not something that's been tested to your knowledge, is it?

A. No. I think as I, as I explained, I think this is -- this is a tool we have now to look at this question but it hasn't been examined.

Q. And it hasn't been subjected to peer review or publication, has it?

A. Correct.

Q. As the evidence exists today, the

generally accepted position in the scientific community is vaccines are not associated with autism, true?

A. True. And the -- the qualifier there is in the scientific community. In the lay community it is quite different. And especially in the among autism parents.

Q. You've encountered in your practice well-intentioned parents who are passionate about this position that vaccines cause autism and they're just in error in your opinion? You've encountered that, haven't you?

A. I think that's overstating it. I think that I don't consider them to be in error, I think that they hold their opinions --

Q. Okay.

A. -- just as people hold political opinions.

Q. I see.

A. And I try to reason with them and I do my best to serve their children.

Q. Have you talked with any doctors pertaining to Yates Hazlehurst case and the opinions you hold?

A. No.

Q. Have you talked, for instance, with Dr. Richard Kelley?

A. I've not spoken with him lately, and I -- I can't recall if I spoke to him previously about Yates.

When we were at Kennedy Krieger together, I would commonly send him -- either send him the patient to see that -- I would commonly screen the patient for lab values and review those lab values with Dr. Kelley, and then I would either send the patient to him or get back to the family after we got the lab result.

Q. We had a conversation earlier about some medical literature that you've provided in this case. And I want to ask another question about that.

The literature that you've supplied to Mr. Smith and he supplied to me in this case, is that all information that you gathered or was some of it sent to you by somebody else?

A. I gathered it.

Q. Okay. Have you ever worked with Mr. Smith before this case?

A. No.

Q. Have you had any conversations with Rolf Hazlehurst?

A. I had email correspondence in the past over, over the years actually. He had approached me several times about testifying and I agreed earlier this year I believe to look at the records and give my opinion. I spoke briefly with him just to -- about sending the records. He agreed to send them on a thumb drive and that's all the correspondence I've had.

Q. I want to mark as Exhibit 10 the email correspondence you've had both with Mr. Hazlehurst and Mr. Smith. You've provided that previously.

(Deposition Exhibit No. 10 marked.)

A. Whatever I provided is --

Q. That's all you have?

A. Right.

Q. Okay. Do you know any of the other attorneys for Mr. Hazlehurst in this case?

A. No, I do not.

Q. A temporal association is not the same

thing as causation, true?

A. True. But we often use in clinical medicine we use temporal associations to give clues to study causation.

Q. Is it true that the manifestations of autism normally manifest about the same time as vaccines are being given in children?

A. That's true.

Q. You made reference earlier to the fact that you had seen Yates Hazlehurst I think in Baltimore?

A. Correct.

Q. Have you looked back at your notes from that encounter?

A. It's been a while. If I could review it.

Q. See if this is your note from October 14, 2002 along with some lab work that was done at that time. Just glance at that and see if you can identify that for us.

(Handing document to witness.)

A. Yes, this is mine.

MR. PHILLIPS: Okay, we'll mark that as Exhibit 11.

(Deposition Exhibit No. 11 marked.)

Q. At the time that you saw Yates Hazlehurst and prepared this note of October 14, 2002, had you reviewed any of his medical records?

A. Yes, briefly.

Q. The information that you described here about Yates's progress and so forth, did that come from your conversations with his parents or paternal grandmother that were with him that day?

A. Yes.

Q. As opposed to gleaning that from the medical record?

A. Yes.

Q. There was -- in what you wrote on October 14th, 2002 there is not any mention of a vaccine, is there?

A. No.

Q. There is not any suggestion that a vaccine played any role in his autistic regression, is there?

A. Not according to the history.

Q. And --

A. I should -- I should add that doesn't mean they didn't tell me there was. Because I frequently would take -- would hear that history but wouldn't necessarily include it in the record.

Q. But if -- you in your note come to a point of making your own assessment and your own conclusions about the patient, right?

A. Correct.

Q. And when you made your own assessment and your own conclusion, you didn't mention vaccines playing any role in any regression, did you?

A. Correct.

Q. There is no discussion here about Yates having had any fever, is there?

A. No.

Q. There is no mention in this note of his having mitochondrial disorder or disease, is there?

A. No. Well, I specifically said he's not had genetic or metabolic testing.

Q. So you did not diagnose him with mitochondrial disorder or disease on this visit,

did you?

A. Not at the time of the visit. We went -- I think as I reviewed the labs, there was question in some of the results that, and I can't recall if I discussed them at the time with Dr. Kelley or -- because he didn't return for follow-up. And I didn't make a note as to whether I contacted the family with the results.

Q. Well, it's true that in this document you prepared to describe your encounter you didn't mention mitochondrial disorder and you didn't mention interpreting any of the labs as being suggestive or conclusive for mitochondrial disorder, true?

A. True.

Q. So in October of 2002 you didn't know that Yates had mitochondrial disorder?

A. Correct.

Q. There is no discussion in this note of the cause of the autism or the alleged regression, is there?

A. Well, we discussed the nature of encephalopathy with regression and development of symptoms. And I, you know, I don't know what

that consisted of.

Q. My question was a little different. There is nothing in the note that outlines any opinion about any cause of the autism in Yates, is there?

A. Not specifically stated. But the testing that I requested would have been looking for signs of a metabolic, underlying metabolic disorder.

Q. Even after getting the results of those tests you didn't make any note that you'd reached a conclusion?

A. No. I didn't -- I don't have a note in the record.

Q. The testing that was done at the time of your encounter in October of 2002 was not interpreted as showing mitochondrial disorder at the time, was it?

A. No.

I believe, I believe I may have sent these results to the family, but I'm not sure. Because I wrote here "common in autism for the elevated AST." I wouldn't have written that for myself.

Q. Did you write any notes on any of the lab works that says "common in mitochondrial disorder" or anything like that?

A. No. I believe there is copies of copies.

Q. Thank you.

Were you able to reach any conclusions from this testing that was done in October of 2002?

A. Not that I recall.

Q. What were you testing for?

A. I was looking for signs of a metabolic disorder, but it's common that we do this testing and we don't see specific findings. I believe Dr. Kelley interpreted, though, the amino acids after that to show.

Q. His name is actually on some of the lab testing, isn't it?

A. Correct.

Q. And he didn't interpret this testing at the time as showing mitochondrial disorder, did he?

A. Not that I recall, no.

Q. Do the medical records themselves show

a regression after February 8th, 2001?

A. I don't recall. I'd have to review it.

MR. PHILLIPS: Were you able to locate the medical record, Bryan?

MR. SMITH: I was not. I was taking notes. I mean, if you want to take a break, I can probably find it.

Q. How difficult would it be for you to retrieve the medical records from the Jackson Clinic that you say you've reviewed?

A. Well, I think they're on here.

Q. So you just need a laptop?

A. Mm-hmm.

MR. PHILLIPS: Can we take a break and do that?

MR. SMITH: Sure.

THE VIDEOGRAPHER: We're now going off the record. This is the end of tape number 1, the time is 10:20 a.m.

(Recess taken.)

THE VIDEOGRAPHER: We're now going back on the record. This is tape number 2, the time is 10:34 a.m.

Q. During the break, Dr. Zimmerman, were you able to retrieve the Jackson Clinic medical records?

A. I was.

Q. Do you have them in front of you?

A. Indeed.

Q. Have you located the August 16th, 2000 visit?

A. Yes, I have.

Q. Is that the date where according to the records he received his six-month vaccines?

A. As I recall, yes.

Q. All right. Look at the next visit after that and see if it is September 5th, 2000?

A. It is.

Q. Read that note and tell me if there is any indication of any vaccine reaction.

A. It says he had a viral upper respiratory infection.

Q. That's not a vaccine reaction, is it?

A. No.

Q. So there is no reference in the September 5th, 2000 note to any reaction to the six-month vaccine, is there?

A. There is no mention of it, no.

Q. There is no -- you mentioned a phrase earlier "inconsolable crying." There is no mention of any inconsolable crying in the September 5th, 2000 note, is there?

A. No, there is not. It says that he fusses with the ear exam but in no distress.

Q. And look at the September 27, 2000 note. Is that the next visit?

A. Yes.

Q. There is no mention of any vaccine reaction in that note either, is there?

A. Says he got sick last Thursday, started with some temp, cold symptoms, getting better until last night. And then they found that he had early otitis media.

Q. No indication of a vaccine reaction in that note either, is there?

A. No notation of it, no.

Q. So having looked at the two office visits after the six-month vaccine was given would you agree that there is no indication in the medical record of any vaccine reaction?

MR. SMITH: Object to the form.

A. Not in the medical record as stated.
Q. You agreed with my statement, right?
A. Correct.
Q. Okay. Now, look at the February 8, 2001 note.
A. Not quite clear where this one starts. Oh, yes, here.
Q. Okay.
A. One-year checkup.
Q. Now, on February 8th, 2001, is that the visit we were discussing earlier where he had his one-year vaccines?
A. It was my understanding he had them at 11 months. He had a purulent effusion in his ear, is red on the right, purulent effusion on the left.
Q. If this will speed us up I'm happy to say this, and I don't think Mr. Smith will disagree, that the vaccines were given on February the 8th, 2001 according to the medical records.
A. Here is the record of, yeah.
Q. So you found the record now?
A. Right.

Q. Okay. Look for the first visit after that which is February 23rd, 2001 I think?

A. Correct.

Q. Is there any evidence on February 23rd, 2001 of any regression?

A. He -- he had a rash from the antibiotic that was changed. Might have asthma and they were concerned. He had no wheezing, possible broncho spasms, went through a trial of Albuterol but, no, there is no mention of regression.

Q. Okay. Look at the April 24th, 2001 note. Do you have that?

A. Yes.

Q. Does that appear to be the next visit?

A. Yes.

Q. Read the note and tell me if there is any evidence of regression.

A. No. Thought he had teething behavior, early otitis, possible early otitis.

Q. But no indication of regression?

A. No.

Q. Look at August 17th, 2001.

A. Okay.

Q. Is there any evidence of regression there?

A. No.

Q. Look at September 20th, 2001.

A. I don't have -- oh, wait. Okay.

Q. Have you found September 20th, 2001?

MR. SMITH: It's Rolf.

MR. HAZLEHURST: Dr. Zimmerman, I apologize for being late.

THE WITNESS: I'm sorry, we're short on chairs.

MR. PHILLIPS: Want to go off the record? Go off the record for just a minute.

THE VIDEOGRAPHER: Now going off the record, the time is 10:42 a.m.

(Recess taken.)

(Rolf Hazlehurst now present.)

THE VIDEOGRAPHER: Now going back on the record, the time is 10:43 a.m.

Q. Look at the September 20th, 2001 office note, please.

A. Yes.

Q. Read that note and tell me if there is any evidence of regression.

A. He's 19 months old, usually fussy the last day or two, sometimes fine and playful, otherwise intermittently cling parent -- to parent and pulls at his ears and gets fussy. Restless in his bed, otherwise no sign of illness. Did not have fever, cold, cough. He's not had a bowel movement since the day before yesterday, but fussiness really started before that. Urinating well. Fussy here in the office, ear drums are normal.

Q. Doesn't it also say fussy in the office but nothing unusual for a one and a half year old?

A. Correct.

Q. Go ahead.

A. Neurologically normal.

Q. So no evidence of regression in that note?

A. No. Not stated, no.

Q. So this note is more than seven and a half -- more than seven months after the vaccine is given on February 8th, 2001, right?

A. Correct.

Q. And so based upon the medical record,

there was not any regression after the vaccine is given on February 8th, 2001, true?

MR. SMITH: Object to form.

A. It's not stated, no.

Q. If the medical records are accurate, would that impact your opinions?

A. Not necessarily. Because oftentimes the routine examinations are not sensitive to the changes in the child and don't -- often don't reflect the developmental progression in the child. But I would -- I would rely on other sources of history.

Q. Isn't the medical record an important source of information for the condition of the child on the date of the visit?

A. Certainly.

Q. And in those notes we looked at up through September 20th, 2001 you didn't see any reference to any inconsolable crying, did you?

A. No.

Q. At what temperature level in a child of say age one to two is it considered a fever? A temperature of what is considered a fever?

A. 99.

Q. Or greater?
A. A hundred.
Q. 99.5 or greater?
A. Right.
Q. Even if Yates Hazlehurst had not had the vaccines on February 8th, 2001, he still likely would have regressed, right?
MR. SMITH: Object to the form.
A. I don't know that. I would -- I would -- I think that would -- that's speculation.
Q. So would it be speculative to say what his course would have been had he not been vaccinated on February 8th, 2001 and everything else about him is the same?
A. Given the fact that we now know that he had mitochondrial, underlying mitochondrial problem, he's more likely than not that the vaccine along with his underlying ear infection predisposed him to regression.
Q. But if we take the vaccine out of the equation and he still has the ear infection and all the other problems, isn't he likely to still have the same outcome?

MR. SMITH: Object to the form.

A. I don't know that.

Q. And we can't know that, can we, with any certainty?

A. Not for certain.

Q. Do you recall testifying in the Madariaga case?

A. Which case?

Q. I may be saying it wrong but I can spell it for you.

MR. SMITH: He knows the girl's name. Alexa Allen.

Q. M-A-D-A-R-I-A-G-A.

A. Alexa Allen, yes.

Q. Okay. You call it the?

A. Alexa Allen was --

Q. Okay.

A. -- her name as I knew of.

Q. Are you familiar with the outcome in that particular proceeding?

A. Yes.

COURT REPORTER: Did you say yes?

THE WITNESS: Yes.

Q. What was the outcome?

A. The petitioner was denied.

Q. And in that case were you giving essentially the same opinion as you're giving in this case?

A. Essentially.

Q. Did you submit a report in that case?

A. As I recall, yes. I also testified in court.

Q. Yes, sir. But is it true that your report in that case contained no statement addressing the role of the MMR vaccine in the development of the patient's condition?

A. I don't recall. I'd have to review it.

Q. Did you testify in the Madariaga case that you could not directly attribute autistic regression to the MMR immunization or any resulting inflammation?

A. I believe I did, yes.

Q. And is that also your opinion in this case?

A. Similar. But, again, it's the current research, current knowledge, combined with our knowledge of the mitochondrial problem.

Q. Did you testify in the Madariaga case that there is an indication that inflammation plays a role in the autism process but the work in this area has produced few definitive answers?

A. Sounds correct.

Q. And that would be your position here today, right?

A. I think we've advanced since then. In the last few years have --

Q. Do you know the date of this, this decision, which is September 2015?

A. The decision came long after the -- the testimony.

Q. What year did you testify?

A. I believe it was two years ago. Would have been '14.

Q. Did you testify in that case that it cannot be said that in any one individual inflammation is the cause of autism?

A. Yes.

Q. Is that your opinion still today?

A. Yes.

Q. Did you testify in the Madariaga case that relatively few causes of regression are

known?

A. True.

Q. Is that your opinion still here today?

A. Yes.

Q. Did you testify that the dynamic biochemical environment has made it difficult to nail down causes of autism with many remaining elusive?

A. True.

Q. Is that still your opinion today?

A. It's becoming less elusive.

Q. But as of today it's still your opinion?

A. Yes.

Q. What are the known causes of regression?

A. Um, there are a number of organic acid problems, various metabolic diseases that and, um, genetic disorders that are associated with regression. And they've been outlined in a couple of recent studies, I'm not sure I submitted those.

Q. Is it -- is it true that in most instances we don't know what causes regression?

A. In most instances, yes.
Q. And how frequently is that the case?
A. I'd say the majority.
Q. When we looked at your note earlier from October the 14th, 2002 when you actually saw Yates Hazlehurst, you made a statement at the end of the note something to the effect that you'd be happy to see him in follow-up or see him in a year or see him as needed. Remember that statement?
A. As I recall, yes.
Q. Did he ever return to you for treatment?
A. No.
Q. Did his parents ever seek you for advice or counsel about his treatment after that visit?
A. No. Not that I recall.
Q. Did you review any MRIs of Yates?
A. No. Not as I recall. Nothing in the record.
Q. Can a patient have encephalopathy without having autism?
A. Yes. Encephalopathy is a very general

term, it just means a problem with brain function.

Q. Is encephalopathy a separate medical condition than autism?

A. It's often used synonymously with autism, especially in the early stages, but it can -- can refer to any brain injury such would cause cerebral palsy, seizures or other disorders.

Q. You've heard of the term mitochondrial autism?

A. Yes.

Q. Is it true that that is not a nationally or internationally recognized condition?

A. Not at this point. There have been a few articles in the --

Q. Excuse me just a minute. Is it true at this point?

A. Yes, at this point.

Q. Okay. That it is not a nationally or internationally recognized condition?

A. Correct.

MR. SMITH: And you can explain.

Q. Yes, go ahead.

A. There are articles appearing in the literature associating mitochondrial disorders with regression.

Q. Would it be fair to say that those articles mention a possible association of those two disease entities?

A. Yes.

Q. It's not been an established link at this point, has it?

A. Correct.

Q. And mitochondrial disorder and autism are in fact separate disease entities, aren't they?

A. Yes, but they -- they can intersect.

Q. On your CV you're listed as an ad hoc reviewer for a number of publications, aren't you?

A. Yes.

Q. Would each of those publications be reliable authorities?

A. In most cases, depending on what they're publishing. And I like to think that the articles I reviewed for them are reliable.

Q. You wouldn't continue to be affiliated with an organization that you thought published inaccurate or invalid articles, would you?

A. Correct.

Q. I've been provided with some information about materials that have been sent to you, but I want to ask you, what materials have you actually reviewed for your work in this case?

A. I reviewed all of Dr. Kelley's notes and his statement, looked at the -- Dr. Frye's notes and his test results, and Dr. Niyazov and his notes and testing, Dr. Corbier's position, or his statement.

Q. His -- Corbier's affidavit?

A. Affidavit. And this would be Dr. Frye's notes and some various articles, the ones I sent you. And this is therapies for mitochondrial disorders, this is association of a DNA mutation, genetic mutation with mitochondrial effects on autism.

Q. You actually have Dr. Kelley's handout material that we've looked at earlier?

A. I've had that from time to time. So

those are the ones I concentrated on and printed off. But I looked at others that were sent to me.

Q. Did any of these that you've mentioned in particular, including Dr. Kelley's report or Dr. Frye's records, Dr. Niyazov's records, Dr. Corbier's affidavit, did they have any impact on your opinions?

A. No, not really. I was most interested in the -- the evidence for mitochondrial problems. And Dr. Frye's notes.

Q. When you looked through the materials, did you conclude that there was or was not a definitive diagnosis of mitochondrial disorder?

A. As -- as close as you can get. There was not a genetic diagnosis but a functional diagnosis. And I think that is one of the problems we're facing in the field where what we're really looking at is more of a functional -- a dysfunctional mitochondrial problem. And we're going to find that a dysfunction more than we're going to find the genetic association, or it may be epigenetic as I was saying before.

Q. Is there still some question about whether Yates has mitochondrial disorder?

A. I don't think so. I think the testing is -- is -- is dramatic. The functional abnormality is dramatic. And it's -- it's just a question of eventually finding the reason for that dysfunction. There may be many, many reasons even within the mitochondria itself.

Q. Still a lot unknown?

A. Very, very much so.

Q. How many times have you reviewed a case as an expert witness?

A. Oh, over the years over a hundred.

Q. How many times have you given depositions as you're doing today?

A. Um, I should say probably a hundred depositions. I've reviewed 150 cases.

Q. Have most of the reviews been for the plaintiff or the defendant?

A. Both.

Q. Do you know how it breaks down?

A. I looked at it several years ago when I was questioned about that and it was close to 50/50.

Q. Of the depositions you've given, how many have been for plaintiffs versus defendants?

A. I think that would be same.

Q. Have you testified at trial before?

A. Yes, I have.

Q. How many times?

A. Ten or 12 times.

Q. Do you know the states from which you've reviewed cases?

A. Tennessee.

Q. We know that, don't we? What others?

A. Kentucky certainly, Connecticut when I lived there, Arkansas, I don't believe -- I had one in North Carolina and -- oh, in Florida.

Q. How about Maryland?

A. Yes, I believe there was one or two. Or one and two -- yeah, a few in Maryland, yes.

Q. Mississippi?

A. Yes. Yes, I believe there was.

Q. Virginia?

A. Yes.

Q. Illinois?

A. Yes.

Q. Rhode Island?

A. Yes.
Q. Wisconsin?
A. That, I don't recall.
Q. How about Massachusetts?
A. Yes.
Q. Tell me what this document is, Doctor.
(Handing document to witness.)
A. This is my case list from 2001 to today.
Q. And is it a list of testimony you've given?
A. These are all cases in which I gave a deposition. Or testified.
Q. Okay.
MR. PHILLIPS: Let's mark the case list as Exhibit 12.

(Deposition Exhibit No. 12 marked.)
MR. PHILLIPS: You can actually have that one.
Q. When you serve as an expert, do you make a charge?
A. Six hundred an hour for, for this.
COURT REPORTER: For what?

THE WITNESS: Six hundred.

Q. So your charge or your charges in this particular case are what?

A. I don't know, I haven't listed that.

Q. No, your rate per hour.

A. Six hundred, 600.

Q. For all work?

A. For review and deposition, yes. Testimony.

Q. And if you testify at trial, at what hourly rate would you charge for that?

A. The same.

Q. Do you have bills in this case that would show us how much time you've spent on it and what the total charges are?

A. I have not tabulated, not -- I would say several hours.

Q. Have you kept track of the time spent anywhere?

A. I made some notes somewhere. I don't --

Q. Where are they?

A. I don't have them. But it would be about, about four hours.

Q. Before your deposition today, is it your testimony that you've spent a total of four hours working on this case?

A. Yes.

Q. You've not prepared any written reports in this case, have you?

A. No, sir.

Q. Or any notes about any review?

A. No.

Q. Do you know how many cases that you have ongoing currently as an expert witness?

A. Three I believe. Three or four.

Q. Have you ever advertised your services as an expert?

A. No.

Q. You're aware of the court order that said that any literature that was to be relied upon was to be provided 14 days before the deposition?

A. I was not aware of that.

Q. Well, did you actually do that? You were asked to provide whatever literature you said supported your opinions and you did that?

A. Yes.

Q. Okay. And you understood the importance of that is so we could have an opportunity to review it before being here today?

A. Of course.

Q. Okay.

And we have discussed that literature generally during the course of our conversation, haven't we?

A. Yes.

MR. PHILLIPS: Do you want to make for record keeping purposes a cumulative or composite exhibit of all those articles provided just so we'll have them with the transcript?

MR. SMITH: If you want to, that's fine.

MR. PHILLIPS: Do you have a strong position?

MR. SMITH: I think why don't we -- instead of doing that, why don't we just do I'll prepare a bibliography of all the stuff that I put in the file instead of making a big, all those -- all that paper. Just a list of all of that if that's okay and we can just attach as an exhibit that has the citations to the articles.

MR. PHILLIPS: And that will be the same thing that was provided before today, right?

MR. SMITH: Yeah.

MR. PHILLIPS: Okay.

MR. SMITH: The ones that I sent to you.

MR. PHILLIPS: Yes.

(Deposition Exhibit No. 13 marked.)

Q. I told you before we started our conversation today, Dr. Zimmerman, that my goal was to learn the opinions you hold in the case and the bases for those opinions. Have you expressed to me the opinions you hold in this case?

A. Yes, I believe so.

Q. And have you also expressed to me the bases for those opinions?

A. Yes.

Q. And if in fact you're asked to come to testify at trial, then the opinions you expect to express at trial would be the same as those you've given here today?

A. Yes.

Q. Okay. Have you given complete responses to my questions today?

A. Yes, I have.

Q. And when you've needed to look at a particular document, have I given you the opportunity to do so?

A. Yes.

Q. And on a personal level, do you feel that I've been professional and respectful with you?

A. Very much so.

Q. Okay.

MR. PHILLIPS: I appreciate your time very much. That's all I have at this time.

THE WITNESS: Thank you.

EXAMINATION BY MR. SMITH:

Q. Let me get you to look at a record that I pulled out of the Jackson Clinic record. It's an office visit from November of 2000 I believe.

A. November 22nd.

Q. All right. And that was not one that Mr. Phillips showed you, is it?

A. Correct.

Q. And if you'll look at the chief complaint part of the medical record, does it reference shaking episodes that Yates has had in the past, not in the past two months but in the past which would correlate about the time that he had the vaccines in August?

A. Yes.

Q. All right. And would that be an indication that Yates had, in the medical records from Dr. Hays, that Yates had a reaction after his six-month vaccination?

A. Yes.

Q. Is it consistent with the history that you've gotten from the parents?

A. Yes.

Q. Um, let's talk a little bit about --

MR. SMITH: Let's mark this as exhibit number -- is this 13? Are we on 13?

MR. PHILLIPS: I think it would be 14.

MR. SMITH: You're right, 13 is a bibliography.

COURT REPORTER: So this is going to be?

MR. SMITH: 14.

MR. PHILLIPS: What is this, Bryan?

MR. SMITH: The disclosure.

(Deposition Exhibit No. 14 marked.)

Q. If you would, Dr. Zimmerman, look at what I've marked as Exhibit No. 14. Just you don't need to read it out loud, but just look over it if you would.

(Handing document to witness.)

A. Yes.

Q. And does Exhibit No. 14 accurately reflect the opinions that you have in this case?

A. Yes.

Q. And are those opinions stated to a reasonable degree of medical certainty?

A. Yes, they are.

Q. We talked about the research that's going on with mitochondrial disorders and its relationship to regressive autism. As I understand it that research is ongoing and has there been some significant developments in the past few years?

A. Yes.

Q. All right. Are you aware of that research?

A. Yes, very much so.

Q. It's my understanding that you've actually reviewed some of that research that's ongoing and talked to other people that are conducting that research?

A. Correct.

Q. In this particular case, you've already said that based on the metabolic testing that was done in this case that it's clear that Yates Hazlehurst has an underlying mitochondrial disorder?

A. Yes.

Q. And is it accepted in your field of pediatric neurologists that underlying mitochondrial disorders can lead to a regressive form of autism?

A. It's generally accepted by people who are aware of the research going on. And -- although it's not generally accepted in the scientific public or by the public.

Q. But it is accepted by other reputable people in your field?

A. Yes.

Q. Who are aware of the current research that's going on in this field?

A. Yeah, especially people who are working in the field of autism and the metabolic problems involved.

Q. And is -- is it those same people, is it -- is it accepted by those people and do other people in your field, reputable physicians in your field, hold the opinion that vaccines can cause the type of inflammatory response that can lead to a regressive autism?

A. Yes.

Q. And you have been involved and testified in cases in the vaccine court?

A. Yes.

Q. And that theory has been accepted by the vaccine court in certain cases that have led to compensation of children who were injured as a result of a vaccine?

A. The only one I'm aware of who was compensated was Poling and I don't believe that actually went to court.

Q. But actually the same theory that you

have in this case was the same theory generally that you had in Poling?

A. Correct.

Q. And it's your understanding that Poling did receive compensation from the vaccine compensation program for a vaccine-related injury that led to autism?

A. Yes.

Q. The opinions that you've expressed in this case are not opinions that you have developed solely for litigation?

A. Absolutely not.

Q. You actually see children in your clinic daily, weekly, with autism that has resulted from an underlying mitochondrial disorder?

A. Yes.

Q. And when you see those children, you go about trying to figure out what may have been the triggering event or the causative event of the regressive autism?

A. Yes.

Q. And in your practice you look at vaccines as one potential cause for a regressive

autism in a child -- in children like Yates?

A. Potential, yes. And then we -- we're trying very hard to treat them.

Q. There is a difference between making a diagnosis based on -- or let me, a better way to say that.

There is a difference between determining a causative link between say vaccines and regressive autism and epidemiologic studies versus making a connection for a particular patient in a clinical setting?

A. Very different approach.

Q. Can you explain that a little bit?

A. Well, an epidemiological study looks at a large group, but it may not be able to detect a small subgroup. And what we're really looking at is a different approach where we go -- we start not from the large group but from the individual.

Q. One thing that Mr. Phillips asked you was about if there had been any testing of this theory. And you've talked about some research that's ongoing. But it would -- there would be -- some of the research, you couldn't take a

subset of kids who had a mitochondrial disorder and then subject some of them to vaccines and others not to vaccines, that would be unethical?

A. Absolutely. Yes.

Q. And so the medicine or the science is now catching up to the point where it does show that in some subset of kids that there is a causal connection between vaccines and regressive autism in these kids that have the underlying mitochondrial disorder?

A. It's not firmly established but that's what we see here, that as a subset who have the mitochondrial dysfunction and history of regression. And what we need to do now, and are doing, is to compare those children to children who regress -- or compare the children who regressed to children who do not regress with autism.

Q. And that's some of the research that's ongoing now?

A. Yes. And then the next step will be to look at the potential association between those children and immunizations. And other factors.

MR. SMITH: Take about -- a short break?

THE VIDEOGRAPHER: Now going off the record, the time is 11:20 a.m.

(Recess taken.)

THE VIDEOGRAPHER: Now going back on the record, the time is 11:27 a.m.

Q. Mr. Phillips asked you some questions about vaccinations and your opinion about vaccinations and as I understood it you said that you are for and advocate that children be vaccinated?

A. Correct.

Q. When you say that you mean, though, that they need to be vaccinated safely and in accordance with CDC guidelines?

A. Correct.

Q. That's what you recommend in your practice?

A. Yes.

Q. And I just want to make sure that we understand sort of the science behind the connection between the autism and vaccines. As I understand it, kids with a mitochondrial

dysfunction are at risk for regressive autism?

MR. PHILLIPS: Object to the leading.

A. Yes.

Q. And the -- there can be some type of triggering inflammatory response that can cause or lead to the regressive autism?

A. Correct.

Q. And those -- that -- that science is accepted by the people in your field?

A. Yes.

Q. Other reputable physicians in your field?

A. Right. People who work in the field of autism see, commonly see a relationship between infections, inflammation and onset of regression.

Q. And vaccines can cause the type of inflammatory response, in fact they're designed to -- to cause the type of inflammatory response that can lead to or trigger a regressive autism?

A. They're designed to lead to an immune response and that may compound the immune response from an infection.

Q. So, in other words, kids who -- who

have this underlying mitochondrial disorder who are -- have an ongoing infection are at an even higher risk of an injury from the vaccine?

A. When combined, yes.

Q. And as I understand it, sort of the key period or where a child's brain is more at risk for these types of, or is more susceptible to these types of risk is somewhere around a year to 18 months?

A. Or 24 months, in that area.

Q. Somewhere in that time frame?

A. Yes. And that -- and that is the time frame when regression commonly occurs.

MR. SMITH: I believe that's all that I have.

RE-EXAMINATION BY MR. PHILLIPS:

Q. Is that the time frame when regression commonly occurs irrespective of the cause?

A. Yes.

Q. With regard to the November 22nd, 2000 Jackson Clinic note about which Mr. Smith asked you, he made reference to some shaking episodes described in that note?

A. Yes.

Q. What could explain those other than a vaccine reaction?

A. Chills, seizures, um, possibly some other gastrointestinal disturbance.

Q. You can't look at that statement about shaking episodes and conclude necessarily that's from a vaccine, can you?

A. No.

Q. In the disclosure, which Mr. Smith marked as Exhibit 14, is that a document you drafted?

A. I reviewed it.

Q. You didn't draft it?

A. No. I've discussed it with Mr. Smith and he sent it to me.

Q. Do you know what materials you had actually reviewed before this disclosure was submitted?

A. Um, no, I don't.

Q. Did you review any disclosures -- I'm sorry. Did you review any materials specific to this case before the disclosure was prepared?

A. I looked at the -- at some of these

records.

Q. Okay. And which ones are we talking about? Dr. Kelley?

A. Yeah, Kelley's and Frye's and Niyazov, yes.

Q. Are those the only records you would have reviewed before the disclosure was prepared?

A. I believe I looked -- I looked through the medical record as well.

Q. Which ones?

A. The original records from that we reviewed today.

Q. From the Jackson Clinic?

A. As I recall, yes.

Q. Okay. If there is any difference between what's set forth in the disclosure and your sworn testimony in the deposition, we should rely upon the sworn testimony you've given today, shouldn't we?

MR. SMITH: Object to the form.

A. I would reserve the right to review --

Q. Sure.

A. -- the difference, yes.

Q. But you've given your sworn testimony

in the deposition today?

A. Yes.

Q. Okay.

In the Poling case about which you were asked, the information that you provided in the Poling case actually was not submitted until after the government settled that case. Did you know that?

A. I don't recall that.

Q. All right.

A. I know that at the time of the Cedillo hearings I was set to testify and I told the government attorneys that I thought there were -- there were possible exceptions. And it was shortly after that that they -- that I -- they wouldn't ask me to testify.

Q. You talked about an inflammatory response some earlier, you remember that discussion?

A. Yes.

Q. Help me understand the potential causes of an inflammatory response.

A. Almost any infection. We commonly see kids this age have frequent ear infections, but

any, any infection really will raise inflammatory response, immune response.

The thing that's different about vaccine reactions is that they occur at different times in children who don't have autism. Any child, they occur at different times. And commonly a reaction to a measles vaccine occurs a week or ten days after it's given. And that's because of the nature of the vaccine.

Q. Other than infections like ear infections, what other causes are there for this inflammatory response?

A. Can you restate that?

Q. Yes, sir. Other than infections such as ear infections, what other potential causes are there for an inflammatory response?

A. Any infection on the skin, in the throat, fever, anything that produces fever.

Q. Can a viral illness produce an inflammatory response?

A. Certainly. Viral or bacterial.

Q. In a child with mitochondrial disorder, can having an infection or a fever or a viral illness lead to regressive autism?

A. Yes.

MR. PHILLIPS: Thank you, I appreciate your time, Dr. Kelley.

THE WITNESS: Zimmerman.

MR. PHILLIPS: I'm sorry, I'm sorry. Dr. Zimmerman. Thank you.

THE WITNESS: Although I appreciate the attribute.

RE-EXAMINATION BY MR. SMITH:

Q. Exhibit No. 14, you've had a chance to review that in the deposition?

A. Yes.

Q. Has your testimony today been consistent with the opinions expressed in Exhibit No. 14?

A. Can I review it once more?

Q. Yeah, absolutely.

A. Yes.

Q. And so regardless of what Mr. Phillips understood or failed to understand about any of the opinions that you gave today, your testimony today has been consistent with the opinions that are expressed in Exhibit No. 14?

A. Yes.

Q. You haven't changed any of those opinions?

A. No.

Q. You still hold those opinions to a reasonable degree of medical certainty?

A. Yes.

Q. And you believe as we sit here today that we have touched on all those opinions at some point in time during the deposition?

A. Yes.

MR. SMITH: That's it.

THE VIDEOGRAPHER: Now going off the record, the time is 11:37 a.m.

(Recess taken.)

THE VIDEOGRAPHER: Now going back on the record, the time is 11:40 a.m.

CONTINUED RE-EXAMINATION BY MR. SMITH:

Q. Mr. Phillips asked you some questions I believe about the Cedillo case?

A. Yes.

Q. Is that right? And it's my understanding that you had written a report in

that case and were set to testify but then were pulled by the U.S. government after you told them that you believe that there were exceptions to the general rule?

A. I don't know that there was a connection between those two events, but that's the way it happened temporally.

Q. In other words, you told them that you felt that there were exceptions like Yates Hazlehurst, kids like Yates and Anna Poling, and other people that actually did have an injury due to vaccines and then after that you were pulled out of the case?

MR. PHILLIPS: Object to the leading and lack of foundation.

Q. Is that true?

A. That's the way it happened, yes.

Q. And Yates would have been one of those kids that would have been the exception to the general rule?

MR. PHILLIPS: Object to leading.

Q. In your opinion?

A. Yes.

MR. SMITH: I think that's it.

RE-EXAMINATION BY MR. PHILLIPS:

Q. What you actually said earlier in response to Mr. Smith was that you had expressed that there were some possible exceptions to the rule, right?

A. Yes.

MR. PHILLIPS: Thank you.

THE VIDEOGRAPHER: Now going off the record. This deposition is concluded, the time is 11:42 a.m.

(The deposition concluded: 11:42 a.m.)

COMMONWEALTH OF MASSACHUSETTS
WORCESTER, SS.

I, STAR GATES CURRY, a notary public in and for the Commonwealth of Massachusetts, do certify that pursuant to appropriate notice of taking deposition, there came before me the subject deponent, who was by me duly sworn; that said witness was thereupon examined under oath and said examination reduced to writing by me; and that the deposition is a true record of the testimony given by the witness.

I further certify that I am not a relative or employee or counsel or attorney for any of the parties, a relative or employee of counsel or attorney, nor am I financially or otherwise interested in the outcome of the action.

Witness my hand and official seal at Worcester, Massachusetts, this 21ST day of November, 2016.

My Commission Expires
March 5, 2021

Star Curry
Notary Public

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IMMUNIZATION SAFETY REVIEW

VACCINES AND AUTISM

Immunization Safety Review Committee
Board on Health Promotion and Disease Prevention

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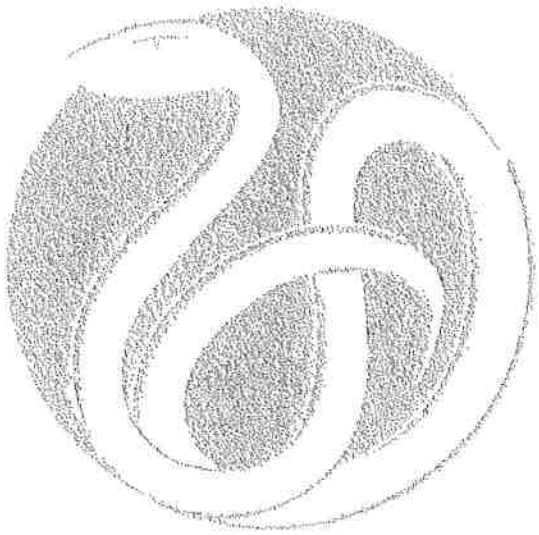
Willing is not enough; we must do."
—Goethe



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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Bradley Doebbeling, Indiana University-Purdue University Indianapolis, Health Services Research Service
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Howard Hu, Harvard University; Brigham and Women's Hospital
Gerald Mandell, University of Virginia Health Center
Peter H. Meyers, George Washington University
Craig Newschaffer, Johns Hopkins University Bloomberg School of Public Health

Richard Rheingans, Emory University, Rollins School of Public Health
Brian Ward, McGill University-Montreal General Hospital
Andrew Zimmerman, Johns Hopkins University

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Robert S. Lawrence,** Johns Hopkins University, and **Floyd E. Bloom,** Scripps Research Institute. Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Foreword

Vaccines are among the greatest public health accomplishments of the past century. In recent years, however, a number of concerns have been raised about both the safety of and the need for certain immunizations. Indeed, immunization safety is a contentious area of public health policy, with discourse around it having become increasingly polarized and exceedingly difficult. The numerous controversies and allegations surrounding immunization safety signify an erosion of public trust in those responsible for vaccine research, development, licensure, scheduling, and policymaking. Because vaccines are so widely used—and because state laws require that children be vaccinated to enter daycare and school, in part to protect others—immunization safety concerns should be vigorously pursued in order to restore this trust.

It is in this context that the Institute of Medicine (IOM) was approached over three years ago by the Centers for Disease Control and Prevention and the National Institutes of Health to convene an independent committee that could provide timely and objective assistance to the Department of Health and Human Services in reviewing emerging immunization safety concerns.

The IOM was chartered by the National Academy of Sciences in 1970 to serve as an adviser to the federal government on issues affecting the public's health, as well as to act independently in identifying important issues of medical care, research, and education. The IOM thus brings to this mission three decades of experience in conducting independent analyses of significant public health policy issues. In particular, as described in more detail in this report, the IOM has a long history of involvement in vaccine safety. The IOM published its first major vaccine safety report in 1977, followed by a subsequent report in 1988; both

focused on the safety of polio vaccines. Two subsequent major reports, published in 1991 and 1994, examined the adverse effects of childhood vaccines. Since then, the IOM has conducted several smaller studies and workshops focused on various vaccine safety topics. These studies were well received by both the public and policymakers, and previous IOM committees on vaccine safety issues have been viewed as objective and credible.

Given the sensitive nature of the present immunization safety review study, the IOM felt it was especially critical to establish strict criteria for committee membership. These criteria prevented participation by anyone with financial ties to vaccine manufacturers or their parent companies, or who had given expert testimony on issues of vaccine safety.

The rationale for imposing these stringent criteria was twofold. First, given growing public concern about vaccine safety and the public scrutiny surrounding this committee's work, it was important to establish standards that would preclude any real or perceived conflict of interest or bias on the part of the committee members. No member has any vested interest in any of the vaccine safety questions that will come before the committee. Second, the IOM wanted to ensure that no committee member had participated in the development or evaluation of a vaccine under study.

Thus, the IOM has convened a distinguished panel of 13 members who are experts in a number of pertinent fields, including pediatrics, neurology, immunology, internal medicine, infectious diseases, genetics, epidemiology, biostatistics, risk perception and communication, decision analysis, public health, nursing, and ethics. The committee members were chosen because they are leading authorities in their respective fields, are well respected by their colleagues, and have no conflicts of interest. This committee brought a fresh perspective to these critically important issues and approached its charge with impartiality and scientific rigor.

As with all reports from the IOM, the committee's work was reviewed by an independent panel of experts. The purpose of the review process is to enhance the clarity, cogency, and accuracy of the final report and to ensure that the authors and the IOM are creditably represented by the report published in their names. The report review process is overseen by the National Research Council's (NRC) Report Review Committee (RRC), comprising approximately 30 members of the National Academy of Sciences, National Academy of Engineering, and IOM. A select panel of reviewers with a diverse set of perspectives are asked to critique the report. Unlike the selection criteria for committee membership, many reviewers will have strong opinions and interests related to the report topic. The composition of the review panel is not disclosed to the committee until after the report is approved for release. While the committee must consider and evaluate all comments from reviewers, it is not obligated to change its report in response to the reviewers' comments. The committee must, however, justify its responses to the reviewers' comments to the satisfaction of the RRC's review monitor and the IOM's review coordinator. A report may not be released to the sponsors or the

public, nor may its findings be disclosed, until after the review process has been satisfactorily completed and all authors have approved the revised draft.

This report represents the unanimous conclusions and recommendations of that dedicated committee whose members deliberated a critical health issue. I am grateful to the committee and its able staff for their efforts on behalf of the public's health.

Harvey V. Fineberg
President, Institute of Medicine

Acknowledgments

The committee would like to acknowledge the many speakers and attendees at its open meeting held on February 9, 2004, at the National Academy of Sciences building in Washington, DC. The discussions were informative and helpful. The committee would also like to thank those people who submitted information to the committee through the mail or via e-mail. Finally, the committee thanks the IOM staff for their dedication to this project. Without their commitment, attention to detail, creativity, sensitivity, and hard work, this project would be unworkable.

Contents

Executive Summary

ABSTRACT

This eighth and final report of the Immunization Safety Review Committee examines the hypothesis that vaccines, specifically the measles-mumps-rubella (MMR) vaccine and thimerosal-containing vaccines, are causally associated with autism. The committee reviewed the extant published and unpublished epidemiological studies regarding causality and studies of potential biologic mechanisms by which these immunizations might cause autism. The committee concludes that the body of epidemiological evidence favors rejection of a causal relationship between the MMR vaccine and autism. The committee also concludes that the body of epidemiological evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism. The committee further finds that potential biological mechanisms for vaccine-induced autism that have been generated to date are theoretical only.

The committee does not recommend a policy review of the current schedule and recommendations for the administration of either the MMR vaccine or thimerosal-containing vaccines. The committee recommends a public health response that fully supports an array of vaccine safety activities. In addition, the committee recommends that available funding for autism research be channeled to the most promising areas. The committee makes additional recommendations regarding surveillance and epidemiological research, clinical

studies, and communication related to these vaccine safety concerns. Please see Box ES-1 for a summary of all conclusions and recommendations.

Immunization to protect children and adults from infectious diseases is one of the greatest achievements of public health. Immunization is not without risks, however. It is well established, for example, that the oral polio vaccine on rare occasion has caused paralytic polio and that vaccines sometimes produce anaphylactic shock. Given the widespread use of vaccines, state mandates requiring vaccination of children for entry into school, college, or day care, and the importance of ensuring that trust in immunization programs is justified, it is essential that safety concerns receive assiduous attention.

At the request of the sponsoring agencies, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH), the Institute of Medicine (IOM) established the Immunization Safety Review Committee to evaluate the evidence on possible causal associations between immunizations and certain adverse outcomes, and to then present conclusions and recommendations. The committee's mandate also includes assessing the broader significance for society of these immunization safety issues.

The specific vaccine safety hypotheses issues examined by the committee are determined by the Interagency Vaccine Group (IAVG), whose members represent several units of the Department of Health and Human Services: the CDC's National Vaccine Program Office, National Immunization Program, and National Center for Infectious Diseases; the NIH's National Institute of Allergy and Infectious Diseases; the Food and Drug Administration (FDA); the Health Resources and Services Administration's National Vaccine Injury Compensation Program; and the Centers for Medicare & Medicaid Services. The IAVG also includes representation from the Department of Defense and the Agency for International Development. The committee has issued seven previous reports on vaccine safety issues over

the three-year study period (2001-2003). This eighth and final report from the committee examines the hypothesis that vaccines, specifically the measles-mumps-rubella (MMR) vaccine and vaccines containing the preservative thimerosal, cause autism. In its first two reports that were published in 2001, the committee examined the hypothesized causal association between the MMR vaccine and autism, and thimerosal-containing vaccines and neurodevelopmental disorders, respectively (IOM, 2001a,b). The IAVG asked the committee to revisit the hypothesized causal association between vaccines and autism in its final report in order to update its conclusions and recommendations based on the significant number of studies that have been undertaken in the last three years.

The committee begins from a position of neutrality regarding the specific immunization safety hypothesis under review. That is, there is no presumption that a specific vaccine (or vaccine component) does or does not cause the adverse event in question. The weight of the available clinical and epidemiologic evidence determines whether it is possible to shift from that neutral position to a finding for causality ("the evidence favors acceptance of a causal relationship") or against causality ("the evidence favors rejection of a causal relationship"). The committee does not conclude that the vaccine does not cause the adverse event

merely because the evidence is inadequate to support causality. Instead, it maintains a neutral position, concluding that the "evidence is inadequate to accept or reject a causal relationship."

The committee's causality assessments must be guided by an understanding of relevant biological processes. Therefore the committee's scientific assessment includes consideration of biological mechanisms by which immunizations might cause an adverse event. The examination of experimental evidence for biological mechanisms has been referred to in previous reports of this committee (IOM, 2001a,b) and others (IOM, 1991, 1994) as an assessment of "biological plausibility." The committee has noted,

however, that the term "biologic plausibility" is a source of confusion on at least two fronts. First, it is associated with a particular set of guidelines (sometimes referred to as the Bradford Hill criteria) for causal inference from epidemiological evidence (Hill, 1965); second, readers sometimes regard the term with a degree of certainty or precision the committee never intended. For example, a relationship between immunization and a particular adverse event may be found to be biologically plausible at the same time that the epidemiological evidence is found to be inadequate to accept or reject a causal relationship.

Given the resulting lack of clarity, the committee adopted a new terminology and a new approach to its discussions of experimental biological data in its third report (IOM, 2002). The committee now reviews evidence regarding "biological *mechanisms*" that might be consistent with the proposed relationship between immunization and a given adverse event.

The biological mechanism evidence reviewed in this report comes from human, animal, and *in vitro* studies of biological or pathophysiological processes. If the committee identifies evidence of biological mechanisms that could be operating, it offers a summary judgment of that body of evidence as weak, moderate, or strong. Although the committee tends to judge biological evidence in humans as "stronger" than biological evidence from highly contrived animal models or *in vitro* systems, the summary judgment of the strength of the evidence also depends on the quantity (e.g., number of studies or number of subjects in a study) and quality (e.g., the nature of the experimental system or study design) of the evidence. Obviously, the conclusions drawn from this review depend both on the specific data and scientific judgment. To ensure that its own summary judgment is defensible, the committee aims to be as explicit as possible regarding the strengths and limitations of the biological data.

In this report, the committee examines the hypothesis of whether the MMR vaccine and the use of vaccines containing the preservative thimerosal can cause autism. Autism is a complex and severe set of developmental disorders characterized by sustained impairments in social interaction,

impairments in verbal and nonverbal communication, and stereotypically restricted or repetitive patterns of behaviors and interests (APA, 1994; Filipek et al., 1999; Volkmar and Pauls, 2003). Over time, research has identified subtle differences in the onset and

progression of autistic symptoms. Autism is classified under the umbrella category of "pervasive developmental disorders" (PDDs) (APA, 2000). PDD refers to a continuum of related cognitive and neurobehavioral disorders that reflects the heterogeneity of symptoms and clinical presentations, and includes autistic disorder, childhood disintegrative disorder, Asperger's syndrome, Rett's syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS, or atypical autism). The term "autistic spectrum disorders" (ASD) has come into common use and is essentially synonymous with the term PDD (Volkmar et al., 2003). In this report, the terms "autism," "autistic," and "autistic spectrum disorders" are used interchangeably to refer to this broader group of pervasive developmental disorders.[1] Although Rett's syndrome is among the autistic spectrum disorders, it is considered by many to be a distinct neurologic disorder and thus its diagnosis is not included in most research that has evaluated the association of the vaccines and autism.

There is considerable uncertainty about the prevalence and incidence of autism and trends over time. Some studies have found an increase, but it is difficult to discern how much of the observed increase is real or possibly due to other factors, such as the adoption of a broader diagnostic concept of autism, improved recognition of autism, or variations in the precision of the studies (Fombonne, 1999, 2003; Gillberg and Wing, 1999).

In the committee's first report, which reviewed the hypothesized causal association between the MMR vaccine and autism (IOM, 2001a), the committee concluded that the evidence at the time favored rejection of a causal relationship at the population level between MMR vaccine and autism. The committee's conclusion did not exclude the possibility that MMR

could contribute to autism in a small number of children because the epidemiological studies lacked sufficient precision to assess rare occurrences; it was possible, for example, that epidemiological studies would not detect a relationship between autism and MMR vaccination in a subset of the population with a genetic predisposition to autism. The biological models for an association between MMR and autism were not established but nevertheless not disproved.

In a subsequent report, the committee reviewed the hypothesized link between thimerosal-containing vaccines (TCVs) and a broad range of neurodevelopmental disorders (NDD), including autism (IOM, 2001b). Thimerosal, an organic mercury compound, has been used as a preservative in some vaccines and other biological and pharmaceutical products since the 1930s. FDA regulations require the use of preservatives in multidose vials of vaccines, except live virus vaccines, to prevent fungal and bacterial contamination (General Biologics Product Stan-

[1] The term "autistic disorder" refers to a more narrow diagnosis defined by criteria in the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV-TR) (APA, 2000).

dards, 2000), which can lead to serious illness and death in recipients. In that report, the committee concluded that the evidence was inadequate to accept or reject a causal relationship between exposure to thimerosal from vaccines and the NDDs of autism, attention deficit hyperactivity disorder (ADHD), and speech or language delay. The committee's causality conclusion was based on the fact that there were no published epidemiological studies examining the potential association between TCVs and NDDs, and the two unpublished, epidemiological studies that were available (Blaxill, 2001; Verstraeten, 2001) provided only weak and inconclusive evidence of an association between TCVs and NDDs. The committee also concluded that the hypothesis linking TCVs with NDDs was not yet established and

rested on incomplete evidence. However, because mercury is a known neurotoxin, and prenatal exposures to methylmercury (a compound closely related to the form of mercury in TCVs) have been documented to negatively affect early childhood development (see NRC, 2000),[2] a potential biological mechanism could be hypothesized based on analogies with this compound.

New epidemiological studies and biological mechanism theories on both issues have emerged since the publication of these IOM reports. In this report, the committee incorporates the new epidemiological evidence and studies of biologic mechanisms relating to vaccines and autism; it does not address the hypothesized link between vaccines and other NDDs.

Until 1999, thimerosal was contained in over 30 vaccines licensed and marketed in the United States, including some of the vaccines administered to infants for protection against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), and hepatitis B. The controversy over thimerosal in vaccines erupted that year, when FDA researchers determined that under the recommended childhood immunization schedule, infants might be exposed to cumulative doses of ethylmercury that exceed some federal safety guidelines established for ingestion of methylmercury, another form of organic mercury (Ball et al., 2001). In July 1999, the American Academy of Pediatrics (AAP) and the U.S. Public Health Service (PHS) issued a joint statement recommending the removal of thimerosal from vaccines as soon as possible (CDC, 1999). With the licensure of a thimerosal-free hepatitis B vaccine in August 1999 and approval of a thimerosal-free preservative hepatitis B vaccine in March 2000, children had access to a hepatitis B vaccine that did not contain thimerosal as a preservative by March 2000. With the FDA approval of a second thimerosal-free version of DTaP vaccine in March 2001, all formulations of vaccines on the U.S. recommended childhood immunization schedule for children 6 years of age or younger became available free of thimerosal used as a preservative (FDA, 2002). Based on information from vaccine

[2] For example, there is evidence that fetal exposure to mercury might lead to detectable differences in neurodevelopmental testing that might be consistent with some neurodevelopmental disabilities (see NRC, 2000).

manufacturers provided to the FDA, the lots of vaccine manufactured before this time that contained thimerosal as a preservative and had been released to the market had expiration dates in 2002 (FDA, 2004). Based on these changes, the maximum amount of mercury from vaccines on the recommended childhood immunization schedule that an infant (less than 6 months of age) can now be exposed to is <3 μg,[3] down from 187.5 μg in 1999 (FDA, 2001, 2004).

The controversy regarding the hypothesized link between the MMR vaccine and autism began in 1998 when Dr. Andrew Wakefield and colleagues published a case series describing 12 children with pervasive developmental disorder associated with gastrointestinal (GI) symptoms and developmental regression (Wakefield et al., 1998). For eight of these children, the onset of their behavioral problems was associated, through retrospective accounts by their parents or physicians, with MMR vaccination. This study put forth a hypothesis that a new phenotype of autism characterized by GI symptoms and developmental regression could be associated with the MMR vaccine. While the authors acknowledged that the study did not prove an association between MMR and the conditions seen in these children, the report generated considerable interest and concern about a possible link between MMR vaccination and ASD--regressive autism in particular. A recent statement from 10 of the original 13 authors states that the data were insufficient to establish a causal link between MMR vaccine and autism (Murch et al., 2004).

Causality Argument

Epidemiological studies examining TCVs and autism, including three controlled observational studies (Hviid et al., 2003; Miller, 2004; Verstraeten et

al., 2003) and two uncontrolled observational studies (Madsen et al., 2003; Stehr-Green et al., 2003), consistently provided evidence of no association between TCVs and autism, despite the fact that these studies utilized different methods and examined different populations (in Sweden, Denmark, the United States, and the United Kingdom). Other studies reported findings of an association. These include two ecological studies[4] (Geier and Geier, 2003a, 2004a), three studies using passive reporting data (Geier and Geier, 2003a,b,d) one unpublished study using Vaccine Safety Datalink (VSD) data (Geier and Geier, 2004b,c), and one

[3] 3μg is the maximum amount that could have been received by an infant in the first 6 months of life if they received trace-containing formulations (e.g., Engerix B hepatitis B vaccine, Tripedia DTaP vaccine) as opposed to those that contain no thimerosal (e.g., Recombivax HB hepatitis B vaccine pediatric formulation, Infanrix DTaP, Daptacel DTaP) (FDA, 2004d).

[4] These studies were classified as ecological because they rely on aggregate data rather than individual-level data to make inferences about causality. However, the authors appear to attempt an individual-level analysis, but it is unclear how this can be, given the data they used. Based on the available information, the study design is indeterminate. See text for more information.

unpublished uncontrolled study (Blaxill, 2001). However, the studies by Geier and Geier cited above have serious methodological flaws and their analytic methods were nontransparent, making their results uninterpretable, and therefore noncontributory with respect to causality (see text for full discussion). The study by Blaxill is uninformative with respect to causality because of its methodological limitations. Thus, based on this body of evidence, **the committee concludes that the evidence favors rejection**

of a causal relationship between thimerosal-containing vaccines and autism. This conclusion differs from the committee's finding in its 2001 report on TCVs and NDDs which was that the evidence was "inadequate to accept or reject a causal relationship between exposure to thimerosal from childhood vaccines and the neurodevelopmental disorders of autism, ADHD, and speech and language delay." (IOM, 2001b, p. 66) The committee's conclusion in 2001 was based on the fact that there were no published epidemiological studies examining the potential association between TCVs and NDDs, and the two unpublished, epidemiological studies that were available (Blaxill, 2001; Verstraeten, 2001) provided only weak and inconclusive evidence of an association between TCVs and NDDs. Furthermore, the conclusion in the 2001 report pertained to a broader set of NDDs, while this report's conclusion applies *only* to autism.

Studies examining the association between MMR and autism, including nine controlled observational studies (DeStefano et al., 2004; DeWilde et al., 2001; Farrington et al., 2001; Fombonne and Chakrabarti, 2001; Madsen et al., 2002; Makela et al., 2002; Takahashi et al., 2003; Taylor et al., 1999, 2002), three ecological studies (Dales et al., 2001; Gillberg and Heijbel, 1998; Kaye et al., 2001), and two studies based on passive reporting system in Finland (Patja et al., 2000; Peltola et al., 1998), consistently showed evidence of no association between the MMR vaccine and autism. Two studies reported findings of a positive association between MMR and autism. The first was an ecological study (Geier and Geier, 2004a) that reported a potential positive correlation between the number of doses of measles-containing vaccine and the cases of autism reported to the special education system in the 1980s. The second was a study of passive reporting data by the same authors (Geier and Geier, 2003c) that reported a positive correlation between autism reports in the Vaccine Adverse Events Reporting System (VAERS) and estimated administered doses of MMR. However, these two studies are characterized by serious methodological flaws and their analytic methods were nontransparent, making their results uninterpretable, and therefore noncontributory with respect to causality (see text for full discussion). The case series study by Wakefield and colleagues (Wakefield et al., 1998), which originally raised the hypothesis linking MMR and

autism, is uninformative with respect to causality. Based on this body of evidence, **the committee concludes that the evidence favors rejection of a causal relationship between MMR vaccine and autism.** This conclusion is consistent with the finding in the committee's previous report on MMR and autism (IOM, 2001a).

Biological Mechanisms

Autism is a very complex disorder. A strong genetic component clearly exists, but there is a growing understanding that environmental factors might be important contributors to the expression of that genetic susceptibility. Animal models (primarily rat models), clinical observations, and pathological data point to an array of possible pathways by which autism develops, though none are proven. Many different pathways might lead to similar expressions, which could account for the multiple presentations of autism.

A link between vaccine components, such as the measles vaccine-strain virus or the ethylmercury preservative thimerosal, is difficult to establish because of the early stage of scientific understanding about the cause(s) of autism. The committee read, and heard presentations at their workshop, about several hypotheses. Data presented to support these hypotheses derive from rodent models of human autism, observations of abnormalities in children with autism or their families, and *in vitro* studies.

One hypothesis about the MMR vaccine involves the presence of measles virus lodging in the intestine of some children, which releases gut-brain mediators or toxins, leading to autism (Wakefield et al., 2002). Another hypothesis related to MMR vaccine is that children with autism have immune abnormalities that are indicative of vaccine-induced-central-nervous system, immune-mediated damage that leads to autism (Singh, 2004).

The thimerosal-related hypothesis is that some genetically susceptible population of children react to the thimerosal in vaccines with increased

accumulation and decreased excretion of mercury from the brain, which alters several key biochemical pathways–for example, apoptosis and DNA metabolism–leading to autism (Bradstreet, 2004). A genetically susceptible subset of children who develop autism following vaccinations is offered as one theoretical explanation for the findings in epidemiological studies of no association between vaccination and autism.

Autism is a heterogeneous syndrome with a broad range of behavioral symptoms and severity. As yet, a biological marker specific for autism has not been defined. It is thus possible that autism encompasses a spectrum of disease subtypes that have different etiologies. This may explain the wide range of immunological abnormalities that have been found in the serum of patients with autism, with some studies reporting evidence of decreased cell-mediated immunity (CMI), and others reporting increased/overactive CMI. Other support for an association of autism with immune dysfunction includes the increased frequency of an extended major histocompatibility complex (MHC) haplotype in autism, increased autoantibodies to brain antigens, and the increased incidence of autoimmune diseases noted in a retrospective study of relatives of people with autism.

However, despite evidence of immune dysregulation in the serum of people with autism, there is as yet no evidence that the immune system plays a direct role

in the neuropathogenesis of autism. Unlike neuroimmunological diseases such as multiple sclerosis, there is no evidence of immune activation or inflammatory lesions in the brains or cerebrospinal fluid of people with autism. This fact also makes it likely that a link with MMR vaccination is circumstantial rather than causal.

It is clear from twin and family studies that there is a strong genetic basis for autism. The recent discovery of the genetic basis of Rett's syndrome, a phenotypically similar NDD with similarly described immunological abnor-

malities, may shed some light on the pathogenesis of autism. Similar epigenetic mechanisms may be operating in autism that lead to simultaneously abnormal development in the immune and central nervous systems.

The hypothesis reviewed by the committee is that vaccine-induced autism represents the end result of a combination of susceptibility (possibly genetic) to immune dysfunction or to abnormal mercury metabolism. Posited intermediate steps include enzymatic abnormalities that might be related to the apoptosis and cellular signaling, leading to an array of behavioral, cognitive, sensory, and motor disturbances. Other environmental exposures have similar effects.

Rodent models suggest that reactions to some infectious agents (e.g., bornavirus and group A streptococcus) lead to somewhat specific neuronal cell death and evidence of autoimmune reactions in the developing and adult brains of rodents. The animals also exhibit abnormal behaviors. These immunological and behavioral findings are similar to those seen in some humans after infection: the behavior in children with PANDAS or in the animal models resembles the behavior constellations in children with autism. A similar set of comparisons can be made with mercury exposures (Bernard et al., 2001), although autism has never been documented as a consequence of high-dose mercury exposure, including acrodynia. While analogies are useful for hypothesis generation, they do not substitute for direct evidence.

Other evidence offered for the vaccine-autism hypothesis includes analogies between rodent behavior and human behavior as well as clinical observations of metabolic or immunologic differences between individuals with autism and normal subjects or subjects with other conditions. In the clinical studies, it is not clear to what extent the abnormalities are antecedents or are comorbid disease expressions, rather than causal factors. That is, it is possible that some people with autism, perhaps even a subgroup that could be identified at some time in the future by genetic markers, also have abnormal immune reactions and abnormal mercury metabo-

lism but that vaccination does not cause these abnormalities, nor do they cause autism.

The committee notes several factors that limit acceptance at this time of the hypothesis that vaccines cause autism. The evidence offered for the hypothesis includes data from *in vitro* experimental systems, analogies between rodent behavior, and human behavior and clinical observations that are at least as well explained as being comorbid disease expressions than as causal factors. That is, it

is possible that some people with autism, perhaps even a subgroup that could eventually be identified by genetic markers, have abnormal immune reactions and abnormal mercury metabolism, but that vaccination of these individuals does not cause these abnormalities or autism itself. However, the experiments showing effects of thimerosal on biochemical pathways in cell culture systems and showing abnormalities in the immune system or metal metabolism in people with autism are provocative; the autism research community should consider the appropriate composition of the autism research portfolio with some of these new findings in mind. However, these experiments do not provide evidence of a relationship between vaccines or thimerosal and autism.

In the absence of experimental or human evidence that vaccination (either the MMR vaccine or the preservative thimerosal) affects metabolic, developmental, immune, or other physiological or molecular mechanisms that are causally related to the development of autism, the committee concludes that the hypotheses generated to date are theoretical only.

SIGNIFICANCE ASSESSMENT

Autism leads to substantial challenges for the families of affected individuals because many people with autism remain dependent throughout their lives. Special education costs can exceed $30,000 per year. The annual

cost of care in a residential school may be as much as $80,000-100,000 (CDC, 1999). In addition to the substantial financial strains, families of children with autism face other demands. During the committees' public session in March 2001 and in the material submitted for the February 2004 meeting, the committee heard about the difficulties of caring for children with autism. Parents described round-the-clock efforts to care for their child, the difficulty of finding knowledgeable and sympathetic health care providers, the challenges in finding high-quality information, and the frustrations of seeing their child change from being active and engaged to being aloof and nonresponsive. Many clinicians, including several committee members, have treated children with autism and witnessed the difficulties and pain experienced by the children and their families.

Although autism is recognized as a serious condition and strides have been made in understanding the disease in many areas, significant gaps remain, particularly regarding its etiology and risk factors. These gaps include uncertainty about prevalence and incidence trends; limited knowledge of the natural history of autism, including its early onset and regressive forms; the lack of a strong biological model for autism; limited understanding of potentially associated features (e.g., immune alterations, enterocolitis); and no current basis for identifying possible subtypes of autism with different pathogeneses related to genetic and environmental interactions. Research has been hindered by changing case definitions and the heterogeneity of study populations that may include cases linked to other known medical risk factors (e.g., Fragile X).

The hypothesis that vaccines, specifically MMR vaccine and the preservative thimerosal, cause autism is among the most contentious of issues reviewed by vaccine safety committees of the IOM. One needs to read just one of the many websites and Internet-based discussion groups on the issue of autism[5] to get a picture of the complicated lives of families with children with autism and the anger of some families toward the federal

government (particularly the CDC and FDA), vaccine manufacturers, the field of epidemiology, and traditional biomedical research. The volume of correspondence to the committee on this issue is impassioned and impressive. There are, however, little data to shed light on how many families believe that vaccination actually caused their child's autism,[6] so that the magnitude of concern in the general population is uncertain. **However, the committee concludes that because autism can be such a devastating disease, any speculation that links vaccines and autism means that this is a significant issue.**

There are many examples in medicine of disorders defined by a constellation of symptoms that have multiple etiologies, and autism is likely to be among them. Determining a specific cause in the individual is impossible unless the etiology is known and there is a biological marker. Determining causality with population-based methods such as epidemiological analyses requires either a well-defined at-risk population or a large effect in the general population. Absent biomarkers, well-defined risk factors, or large effect sizes, the committee cannot rule out, based on the epidemiological evidence, the possibility that vaccines contribute to autism in some small subset or very unusual circumstances. However, there is currently no evidence to support this hypothesis either.

The committee concludes that much more research must be conducted on autism. However, research should be directed towards those lines of inquiry most supported by the current state of knowledge. The vaccine hypotheses are not currently supported by the evidence. Much remains unknown about the etiology or etiologies of autism. Furthermore, there have not been many studies on treatments for autism. Research should be directed towards better understanding the etiology or etiologies of autism and on treatments for autism.

While the committee strongly supports targeted research that focuses on better understanding the disease of autism, from a public health perspective the committee does not consider a significant investment in studies of the theoretical vaccine-autism connection to be useful at this time. The

nature of the debate about vaccine safety now includes the theory by some that genetic susceptibility makes vaccinations risky for some people, which calls into question the appropriateness of a public health, or universal, vaccination strategy. However, the benefits of vaccination are proven and the hypothesis of susceptible populations is

[5] See http://health.groups.yahoo.com/group/Autism-Mercury/messages.

[6] Over three thousand families have filed claims for compensation for autism with the Vaccine Injury Compensation Program (VICP).

presently speculative. Using an unsubstantiated hypothesis to question the safety of vaccination and the ethical behavior of those governmental agencies and scientists who advocate for vaccination could lead to widespread rejection of vaccines and inevitable increases in incidences of serious infectious diseases like measles, whooping cough, and Hib bacterial meningitis.

The committee encourages that research on autism focus more broadly on the disorders' causes of and treatments for it. Thus, **the committee recommends a public health response that fully supports an array of vaccine safety activities. In addition the committee recommends that available funding for autism research be channeled to the most promising areas.**

The committee emphasizes that confidence in the safety of vaccines is essential to an effective immunization program–one that provides maximum protection against vaccine-preventable diseases with the safest vaccines possible. Questions about vaccine safety must be addressed responsibly by public health officials, health professionals, and vaccine manufacturers. Although the hypotheses related to vaccines and autism will remain highly salient to some individuals, (parents, physicians, and researchers), this

concern must be balanced against the broader benefit of the current vaccine program for all children.

RECOMMENDATIONS FOR PUBLIC HEALTH RESPONSE

Specific recommendations regarding policy review, epidemiologic research and surveillance, and communication follow. The committee also revisits and discusses many of the recommendations of its two previous reports on vaccines and autism (IOM, 2001a,b).

Policy Review

- **At this time, the committee does not recommend a policy review of the licensure of MMR vaccine or of the current schedule and recommendations for the administration of the MMR vaccine.**

- **At this time, the committee does not recommend a policy review of the current schedule and recommendations for the administration of routine childhood vaccines based on hypotheses regarding thimerosal and autism.** Currently, thimerosal has been removed from all universally recommended childhood vaccines except influenza vaccine. A thimerosal-free version of the influenza vaccine exists, however, and is available for use in infants, children, and pregnant women. There are a few vaccines with thimerosal (e.g., Td) that infants and young children[7] could be exposed to, but only under very special circumstances.

[7] Td is recommended for children 12-18, but it is conceivable that some infants and young children could receive Td in lieu of DTaP.

- The committee also recommended in its prior report that the appropriate professional societies and government agencies review their policies on the non-vaccine biological and pharmaceutical products that contain thimerosal and are used in infants, children, and pregnant women. The committee's recommendation reflected concern about total mercury burden and potential risk of certain NDDs. While the United States chose to eliminate thimerosal from routine childhood vaccines as a precautionary measure and because it was feasible, the committee recognizes that other countries have different constraints and other factors; their own assessments of the risks and benefits may lead those countries to reach different conclusions regarding the thimerosal content of their vaccines. **Given the lack of direct evidence for a biological mechanism and the fact that all well-designed epidemiological studies provide evidence of no association between thimerosal and autism, the committee recommends that cost-benefit assessments regarding the use of thimerosal-containing versus thimerosal-free vaccines and other biological or pharmaceutical products, whether in the United States or other countries, should not include autism as a potential risk.**

Surveillance and Epidemiologic Research

- **The committee reaffirms its previous recommendation to use standard and accepted case definitions and assessment protocols for ASD to enhance the precision and comparability of results from surveillance, epidemiological studies, and biological investigations. Studies should also address the heterogeneity in the etiology of ASD and the spectrum of clinical presentation.**

- **The committee reaffirms its previous recommendation to conduct clinical and epidemiological studies of sufficient rigor to identify risk factors and biological markers of ASD in order to better understand genetic or environmental causes of ASD.**

- **Surveillance of adverse events related to vaccines is important and should be strengthened in several ways:**
  - **The committee recommends that standardized case definitions for adverse events be adopted.**
  - **The committee recommends that formal guidelines or criteria be developed for using VAERS data to study adverse events.**
  - **The committee recommends the continued use of large-linked databases, active surveillance, and other tools to evaluate potential vaccine-related adverse events.**
  - **The committee supports the development of Clinical Immunization Safety Assessment (CISA) centers to improve understanding of adverse events at the individual level.**

- Many of the epidemiological research recommendations of the committee's 2001 report on thimerosal and NDDs are either under way or have been completed. **Insofar as monitoring of ASD occurs, one area of complementary research that the committee continues to recommend is surveillance of ASD as exposure to thimerosal declines.** Any research in this area should be conducted with critical attention to case definition, diagnostic criteria, and other factors (for example, data collection procedures and definitions of autism in the special education system) that could affect prevalence estimates of ASD.
- Little is known about the levels of background exposure to mercury in the population. **The committee recommends increased efforts to quantify the level of prenatal and postnatal exposure to thimerosal and other forms of mercury in infants, children, and pregnant women.**

Clinical Studies

- The committee heard from some parents of children with ASD who have chosen to rely on chelation therapy as a treatment. The committee saw no scientific evidence, however, that chelation is an effective therapy for ASD or is even indicated in these circumstances. Chelation therapy is currently indicated only for high-dose, acute mercury poisonings. **Because chelation therapy has potentially serious risks, the committee recommends that it be used only in carefully controlled research settings with appropriate oversight by Institutional Review Boards protecting the interests of the children who participate.**

Communication

Many parents described to the committee their concerns about the MMR vaccine and thimerosal use in vaccines. Many expressed their frustration and difficulties in making informed decisions about vaccination of their children as their level of trust in the government, media, and science in general has declined. Because of the importance and difficulty of maintaining mutual trust, a model that focuses on increasing public participation in risk decisionmaking is likely to make that process more democratic and improve the relevance and quality of the technical analysis (Slovic, 1999). Such participative processes may not necessarily lead to increased acceptability of risk policies, but may lead to higher quality decision-making processes (Arvai, 2003). However, better risk-benefit communication requires attention to the needs of both the scientific and public communities. Many scientists need to develop a more comprehensive understanding of what risk-benefit communication entails and the rich knowledge base that can be used to design strategic communication programs. Appreciating that risk-benefit communication requires two-way exchanges of information and opinions (NRC,

1989) and working from a larger frame of communication methods, scientists will be able to work more effectively with the public to address vac-

cine-related issues. A mix of information, dissemination, education services, and community-based dialogues are probably needed (NRC, 1989).

To address these goals, **the committee recommends developing programs to increase public participation in vaccine safety research and policy decisions and to enhance the skills and willingness of scientists and government officials to engage in constructive dialogue with the public about research findings and their implications for policy development.** Programs such as Project LEAD®, COPUS Grant Schemes, or the IOM Vaccine Safety Forum may serve as useful models. Any proposed program should be easily accessible to the public and should involve a wide range of individuals. Additionally, ways to rebuild trust between the public, scientists, professionals, media, and government should be explored.

BOX ES-1
Committee Conclusions and Recommendations

SCIENTIFIC ASSESSMENT

Causality Conclusions

The committee concludes that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism.

The committee concludes that the evidence favors rejection of a causal relationship between MMR vaccine and autism.

Biological Mechanisms Conclusions

In the absence of experimental or human evidence that vaccination (either the MMR vaccine or the preservative thimerosal) affects metabolic, developmental, immune, or other physiological or molecular mechanisms that are causally related to the development of autism, the committee concludes that the hypotheses generated to date are theoretical only.

SIGNIFICANCE ASSESSMENT

The committee concludes that because autism can be such a devastating disease, any speculation that links vaccines and autism means that this is a significant issue.

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

The committee recommends a public health response that fully supports an array of vaccine safety activities. In addition the committee recommends that available funding for autism research be channeled to the most promising areas.

Policy Review

At this time, the committee does not recommend a policy review of the licensure of MMR vaccine or of the current schedule and recommendations for the administration of the MMR vaccine.

At this time, the committee does not recommend a policy review of the current schedule and recommendations for the administration of routine childhood vaccines based on hypotheses regarding thimerosal and autism.

Given the lack of direct evidence for a biological mechanism and the fact that all well-designed epidemiological studies provide evidence of no association between thimerosal and autism, the committee recommends that cost-benefit assessments regarding the use of thimerosal-containing versus thimerosal-free vaccines and other biological or pharmaceutical products, whether in the United States or other countries, should not include autism as a potential risk.

Surveillance and Epidemiologic Research

The committee reaffirms its previous recommendation to use standard and accepted case definitions and assessment protocols for ASD to enhance the pre-

cision and comparability of results from surveillance, epidemiological studies, and biological investigations. Studies should also address the heterogeneity in the etiology of ASD and the spectrum of clinical presentation.

The committee reaffirms its previous recommendation to conduct clinical and epidemiological studies of sufficient rigor to identify risk factors and biological markers of ASD in order to better understand genetic or environmental causes of ASD.

Surveillance of adverse events related to vaccines is important and should be strengthened in several ways:

The committee recommends that standardized case definitions for adverse events be adopted.

The committee recommends that formal guidelines or criteria be developed for using VAERS data to study adverse events.

The committee recommends the continued use of large-linked databases, active surveillance, and other tools to evaluate potential vaccine-related adverse events.

The committee supports the development of Clinical Immunization Safety Assessment (CISA) centers to improve understanding of adverse events at the individual level.

One area of complementary research that the committee continues to recommend is surveillance of ASD as exposure to thimerosal declines.

The committee recommends increased efforts to quantify the level of prenatal and postnatal exposure to thimerosal and other forms of mercury in infants, children, and pregnant women.

Clinical Studies

Because chelation therapy has potentially serious risks, the committee recommends that it be used only in carefully-controlled research settings with appropriate oversight by Institutional Review Boards protecting the interests of the children who participate.

Communication

Better risk-benefit communication requires attention to the needs of both the scientific community and public communities. Many scientists need to develop a more comprehensive understanding of what risk-benefit communication entails and the rich knowledge base that can be used to design strategic communication programs. Thus, the committee recommends developing programs to increase public participation in vaccine safety research and policy decisions and to enhance the skills and willingness of scientists and government officials to engage in constructive dialogue with the public about research findings and their implications for policy development.

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American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Updated April 2013

Vaccine Safety: Examine the Evidence

The safety and effectiveness of vaccines are under constant study. Because vaccines are designed to be given routinely during well-child care visits, they must be extraordinarily safe. Safety testing begins as soon as a new vaccine is contemplated, continues until it is approved by the FDA, and is monitored indefinitely after licensure. The American Academy of Pediatrics (AAP) works closely with the Centers for Disease Control and Prevention (CDC) to make recommendations for vaccine use.

Over the past decade, questions have been raised regarding a relationship between autism and vaccines. Along with general safety concerns, parents have wondered about:

- too many vaccines overwhelming the immune system;
- the measles, mumps, rubella combination vaccine (MMR); and
- the preservative thimerosal, which was never present in MMR but was present in several vaccines used in the 1990s, but has since been removed from all routinely used childhood vaccines with the exception of flu.

Research has been conducted on all of these topics, and the studies continue to find vaccines to be a safe and effective way to prevent serious disease. This document lists those studies and provides links to the publications to allow parents and all those who administer or recommend vaccines to read the evidence for themselves. These studies do not show any link between autism and MMR vaccine, thimerosal, multiple vaccines given at once, fevers or seizures. This is not an exhaustive list- vaccine safety studies are constantly being conducted and published and may not be reflected here.

Please examine the evidence for yourself. If you have any questions, speak with your pediatrician.

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Facts for Parents About Vaccine Safety

Why are vaccines important?

Immunizations protect children. Vaccine-preventable diseases can have dangerous consequences, including seizures, brain damage, blindness and even death. Because of the success of the national immunization program, many young parents today have never seen a case of one of these illnesses, but measles, meningitis, chickenpox, pertussis and other diseases exist in the world and would re-emerge here if immunization rates fell. For example, recent outbreaks of measles in the U.S. were traced to unvaccinated children who became infected while traveling in Europe. Likewise, it would only take one case of polio from another country to bring the disease back to the U.S. if children are not protected by vaccination.

Are vaccines safe?

Yes. Today's vaccines are safer than any in history. Vaccines contain antigens, which are either live but very weakened viruses, inactivated viruses, or small parts of bacteria or viruses that prompt the body to produce protective antibodies without causing the disease. Even though children receive more vaccines now, the total number of antigens is less because today's vaccines are more refined than older versions. At a very young age, children's immune systems are equipped to respond to many antigens at the same time, including those in vaccines as well as the ones they encounter in their daily activities such as eating, breathing and playing.

In addition to antigens, vaccines contain ingredients to prevent contamination and improve effectiveness. These ingredients have been found to be safe in humans in the quantities given in vaccines, which is much less than children are exposed to in their environment, food and water. Valid scientific studies have shown there is no link between autism and thimerosal, a mercury-based preservative once used in several vaccines (and still used in some flu vaccine). However, since thimerosal was removed from childhood vaccines in 2001, autism rates have actually increased, supplying further evidence that thimerosal does not cause autism.

Before a vaccine is licensed, it is studied in thousands of children and in combination with other vaccines. After licensure, the federal government continues to monitor a vaccine's safety. This continuous monitoring ensures researchers will uncover any rare side effects, even if they affect only a small number of children. For example, a rotavirus vaccine was withdrawn in 1999 after it was linked to intestinal blockages in about 100 children. This vaccine was replaced by a new and safer product. Today's recommended vaccines have been shown to be safe and effective for millions of children.

Can I delay or skip vaccines?

It is not a good idea to skip or delay vaccines, as this will leave your child vulnerable to diseases for a longer time. Children are most vulnerable to complications from disease in their early years of life, when vaccines provide protection, and some vaccines produce a better immune response at particular ages. Parents should follow the schedule provided by the U.S. Centers for Disease Control and Prevention, the American Academy of Pediatrics and the American Academy of Family Physicians, which is designed by experts to ensure maximum protection and safety for children at various ages. This schedule allows for some flexibility to delay certain shots when advised by a child's pediatrician due to illness, certain chronic conditions or other medical reasons. Parents should discuss any concerns with their child's pediatrician.

More information is available at www.aap.org/immunization and www.cdc.gov/vaccines.

June 2008

<LINK: https://my.clevelandclinic.org/ >

Cleveland Clinic

Diseases & Conditions

Myths and Facts About Mitochondrial Diseases

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MYTH

Mitochondrial disease <LINK: https://my.clevelandclinic.org/services/neurological_institute/pediatric-neuroscience/pediatric-neurology/diseases-conditions/mitochondrial-disease > is a childhood disease.

FACT

Although mitochondrial disorders are commonly seen in infants and children, they can occur at any age.

MYTH

An individual with mitochondrial disease has mental retardation, growth problems, and/or seizures.

FACT

Only some individuals have these developmental problems <LINK: https://my.clevelandclinic.org/childrens-hospital/specialties-services/departments-centers > . Patients' symptoms can range from extremely mild to severe, involve one or more body systems, and can emerge at any age. The brain, muscles, heart, liver, nerves, eyes, ears and kidneys are the organs and tissues most affected. Most patients' symptoms fluctuate over the course of their disease -- at times experiencing no or few symptoms while at other times experiencing many and/or severe symptoms. Even family members with the same disorder can experience vastly different symptoms.

MYTH

Mitochondrial diseases are inherited only from your mother.

FACT

Not true. There are several ways mitochondrial diseases can be inherited (passed along from parents to children). Under normal circumstances, a person's 'blueprint' -- the DNA in our genes that makes each of us unique, comes from *both* our mother and our father. In mitochondrial diseases, these genes have *mutated* (which means they have changed/become defective; they are not normal.) Instead of receiving pairs of normal genes from each parent, persons with mitochondrial diseases receive *mutated* genes from *each* parent or a *mutated* gene from *only one* parent.

Another way a mitochondrial disease can be inherited is, in fact, only from the mother. In this type, there is a mutation in the mitochondrial DNA - a special DNA that exists only in the mitochondria. Only mitochondrial disorders caused by mutations in the mitochondrial DNA are exclusively inherited from mothers.

MYTH

If parents don't have any symptoms of a mitochondrial disease, there's no chance that their children can have a mitochondrial disease.

FACT

Parents can be 'genetic carriers' of a mitochondrial disease. This means that each parent has inherited a defective gene but do not show symptoms of the disease. However, 'carriers' are able to pass the defective gene onto their children.

Here's an example using parents who are both carriers and have four children. One out of the four children would inherit the defective gene and develop a mitochondrial disease and show symptoms. Two out of the four children will be genetic carriers of a mitochondrial disease, just like their parents. The remaining child would be 'genetically 'typical.' Both the genetically 'typical' patient and the carriers would not develop mitochondrial disease).

MYTH
Since mitochondrial diseases are incurable, no treatments can be given to these patients.

FACT
Even though these disorders are long term and incurable, treatments are available. Early treatment of symptoms can reduce symptoms or slow the decline in health. Avoiding certain medications and medical stressors that worsen symptoms is also helpful. Certain medications and supplements may improve mitochondrial disease-related symptoms -- just as they do for other incurable diseases -- such as diabetes and emphysema.

MYTH
A muscle biopsy is the "gold standard" for diagnosis of mitochondrial disease.

FACT
Although the muscle biopsy is a powerful diagnostic tool <LINK: https://my.clevelandclinic.org/services/neurological_institute/neuromuscular-center/diagnostics-testing > , it should not be considered a "gold standard." A biopsy examination includes microscopic evaluation, enzyme testing <LINK: https://my.clevelandclinic.org/services/heart/diagnostics-testing/laboratory-tests/enzyme-protein-blood-tests > , and genetic testing <LINK: https://my.clevelandclinic.org/services/genomics-genetics/appointments/considering-genetic-testing > . Although all U.S. labs that offer muscle biopsy meet strict laboratory guidelines, there is no agreed-upon standard approach for enzyme testing. Furthermore, a muscle biopsy with full analysis costs well over $10,000 and poses both surgical and anesthetic risks. In some patients, the diagnosis can be made based on clinical symptoms and a positive blood test (identifying a genetic mutation) or a combination of clinical findings and other non-invasive testing. In either case, a muscle biopsy is not necessary. Finally, since biopsy results usually do not alter the long-term outcome or treatment considerations, some specialists and patients choose to treat without the need for a muscle biopsy.

MYTH
Immunizations can be harmful to children with mitochondrial diseases.

FACT
There is no clear evidence that immunizations themselves hurt patients with mitochondrial or metabolic disorders.

Medical stress (fever, dehydration, illness, revving up the immune system) may bring out or worsen metabolic disorders. Thus, there have been some patients where the fever after an immunization led to symptom onset or worsening. In these individuals, it was not the immunization itself that caused these problems. It is generally believed that patients should get their immunizations. Still, for individuals whose symptoms emerge or worsen when under medical stress, spacing out immunizations and tight fever-control may help. (This approach is not based in medical science. It's based solely on reports or observations, which do not provide absolute proof.)

MYTH
All mitochondrial diseases are known by acronym abbreviations (e.g., MELAS, MERRF, NARP, LHON).

FACT
Acronyms were commonly used when these disorders were first described. Today, the naming of mitochondrial disorders is evolving. Mitochondrial disorders are currently named by any of the following methods:

- By acronym descriptions (still in use although most people with a mitochondrial disorder do not have an "acronymic-named" disorder)
- By a name based on a person who described the disease
- By a name based on a specific genetic mutation
- By a name based on a microscopic description of tissue, or
- By a name based on the deficient enzyme

It is important to note that the labels given this disorder do not, in and of themselves, predict the long-term outcome or alter treatment.

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Mitochondrial Disease in Autism Spectrum Disorder Patients: A Cohort Analysis

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Abstract

Background: Previous reports indicate an association between autism spectrum disorders (ASD) and disorders of mitochondrial oxidative phosphorylation. One study suggested that children with both diagnoses are clinically indistinguishable from children with idiopathic autism. There are, however, no detailed analyses of the clinical and laboratory findings in a large cohort of these children. Therefore, we undertook a comprehensive review of patients with ASD and a mitochondrial disorder.

Methodology/Principal Findings: We reviewed medical records of 25 patients with a primary diagnosis of ASD by DSM-IV-TR criteria, later determined to have enzyme- or mutation-defined mitochondrial electron transport chain (ETC) dysfunction. Twenty-four of 25 patients had one or more major clinical abnormalities uncommon in idiopathic autism. Twenty-one patients had histories of significant non-neurological medical problems. Nineteen patients exhibited constitutional symptoms, especially excessive fatigability. Fifteen patients had abnormal neurological findings. Unusual developmental phenotypes included marked delay in early gross motor milestones (32%) and unusual patterns of regression (40%). Levels of blood lactate, plasma alanine, and serum ALT and/or AST were increased at least once in 76%, 36%, and 52% of patients, respectively. The most common ETC disorders were deficiencies of complex I (64%) and complex III (20%). Two patients had rare mtDNA mutations of likely pathogenicity.

Conclusions/Significance: Although all patients' initial diagnosis was idiopathic autism, careful clinical and biochemical assessment identified clinical findings that differentiated them from children with idiopathic autism. These and prior data suggest a disturbance of mitochondrial energy production as an underlying pathophysiological mechanism in a subset of individuals with autism.

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Introduction

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impaired social interaction and communication, as well as isolated interests and repetitive or stereotyped behaviors [1]. ASDs pose a significant burden to affected individuals, their families and society. This burden comes both from the debilitating and lifelong nature of ASDs and from their prevalence. It is now estimated that about one out of every 166 children is affected with ASD [2]. Most cases are idiopathic, although there are many uncommon or rare genetic and metabolic causes of autism that are increasingly recognized [3–5].

In 1998, Lombard postulated mitochondrial dysfunction as a cause of autism [6]. Prior and subsequent case reports provided biochemical data indicating perturbation of mitochondrial energy metabolism in some individuals with ASD [7–12], including mtDNA mutations in several [10,13,14]. Recently, Oliveira and colleagues published a population-based survey of school-age children with ASD. They found that 7% of those who were fully tested met criteria for definite mitochondrial respiratory chain disorders and were also clinically indistinguishable from other children with ASD [15]. This work is notable because it suggests that mitochondrial disorders of energy production may be present in a substantial percentage of children with ASD. To better describe the clinical spectrum of children with 'mitochondrial autism', we undertook a chart review of the biochemical, genetic, and histopathological findings in 25 patients with ASD who had unequivocal evidence of a disorder of oxidative phosphorylation.

Methods

Subject Determination

We reviewed medical records of 25 children with a diagnosis of ASD according to DSM-IV-TR criteria [16] and evidence of a disorder of mitochondrial energy metabolism evaluated by one of our investigators at Cleveland Clinic, Massachusetts General Hospital/LADDERS Program, or Kennedy Krieger Institute. The study was approved by the Institutional Review Boards (IRBs) of these institutions and is in accord with the principles of the Declaration of Helsinki. The IRBs determined that this chart review study met criteria for waiver of consent.

Children were referred for genetic and/or metabolic evaluation of autism but not specifically for evaluation for mitochondrial disease. Children with known chromosomal or monogenic disorders were excluded. All patients met criteria for probable or definite mitochondrial disease by both the Modified Walker Criteria and the Mitochondrial Disease Criteria (MDC) [17,18]. All patients also had either: (1) <20% activity of one or more muscle or fibroblast electron transport chain (ETC) activities; (2) <2 standard deviations below the control mean of one or more ETC complexes by polarographic analysis; (3) a mitochondrial DNA sequence variant of probable pathogenicity plus biochemical evidence of mitochondrial dysfunction; or (4) clinical and biochemical data consistent with a mitochondrial disorder and a sib with enzyme-defined ETC dysfunction. One patient was reported earlier [12].

Clinical and Biochemical Data

Medical records of each patient were independently reviewed by at least two members of the study team. Growth parameters were evaluated using the ABase software and North American pediatric reference values [19]. Institution specific reference intervals were used for assessments of blood lactate and pyruvate, plasma alanine, urinary organic acids, CK, AST, and ALT. Biochemical evidence of mitochondrial ETC dysfunction included increased blood lactate and pyruvate levels, elevated plasma alanine level, and increased urinary levels of Krebs cycle intermediates or 3-methylglutaconate.

Pathology and Enzyme Data

Twenty-three of the 25 children underwent quadriceps muscle biopsies, 11 had skin biopsies, and one had a liver biopsy. Three patients had sibs with muscle biopsies. Muscle ETC determinations were performed at either Horizon Molecular Medicine, LLC, Atlanta [20,21] or the Center for Inherited Disorders of Energy Metabolism (CIDEM) Lab, Cleveland [22]. Muscle biopsy specimens were either snap frozen then shipped for ETC determination in homogenates or muscle mitochondria were isolated from fresh muscle biopsy specimens with aliquots frozen for subsequent determination of ETC activities. Functional (polarographic) analyses of oxidative phosphorylation using freshly isolated muscle mitochondria were performed at CIDEM [22]. ETC determinations of skin fibroblasts were done at CIDEM [23] or Mayo Laboratories. Fibroblast lactate and pyruvate measurements were performed at The Hospital for Sick Children, Toronto [24]. ETC activities were normalized to the mitochondrial marker enzyme citrate synthase, or if citrate synthase activity was not assayed, the percent of the mean of controls was used.

Mitochondrial DNA (mtDNA) Mutation Data

Sixteen of 25 children underwent analyses for selected mitochondrial mutations and 11 of 25 patients had mtDNA mutation analysis by dHPLC of the entire mitochondrial genome at Transgenomic, Inc, Omaha [25]. Each DNA sequence variant was evaluated for pathogenicity by a search of the MITOMAP and mtDB-Human Mitochondrial Genome databases [26,27], PubMed, and compendia of mtDNA mutations including guidelines for determination of pathogenicity [28,29].

Results

Clinical Characteristics of Subjects (Table 1; Tables S1, S2, S3)

Twenty-five patients–13 males and 12 females ages 2–20 years were included in this analysis; 11 patients met DSM-IV-TR criteria for autistic disorder and 14 met DSM-IV-TR criteria for PDD-NOS. Twenty-one patients had definite mitochondrial disease and four had probable mitochondrial disease by the Modified Walker Criteria. Eleven patients met criteria for definite mitochondrial disease and 14 met criteria for probable disease using the MDC.

Table 1. Medical History and Physical Examination.

	Number of patients	Percent of patients
Multiple gestation birth	8	32
Prenatal or perinatal complications	13	52
Cardiovascular abnormality	7	28
GI dysfunction	16	64
GI dysfunction other than reflux or constipation	5	20
Hematologic abnormality	2	8
Endocrine dysfunction	2	8
Renal dysfunction	2	8
Growth retardation (<2 SD for weight and/or height)	5	20
Microcephaly (<2 SD)	4	16
Macrocephaly (>3 SD)	4	16
Fatigability/exercise intolerance	17	68
Marked developmental gross motor delays*	8	32
Seizures	5	20
Movement disorders	2	8
Oculomotor abnormality	4	16
Ptosis	2	8
Sensorineural hearing deficit	3	12
Dysarthria	3	12
Multiple regressions	9	36
Regression(s) after three years of age	6	24
At least 1 major clinical finding uncommon in ASD**	24	96
At least 1 non-CNS organ system involved	21	84
At least 2 non-CNS organ systems involved	8	32
At least 1 neurologic finding uncommon in ASD†	15	60

*Defined as ≥5 SD from mean age at walking [33].

**Does not include multiple gestation birth, prenatal/perinatal complications, GERD, constipation or macrocephaly.

†Does not include fatigability, non-refractory seizures, macrocephaly or regression.

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Twenty-one patients had histories of major non-neurological medical problems, most commonly of the gastrointestinal system, with gastroesophageal reflux affecting nine and constipation affecting eight subjects. Seven patients had structural or functional cardiovascular abnormalities. In addition, 17 patients had excessive fatigability or exercise intolerance and several children had abnormal physical exam findings including six with facial dysmorphism, four with microcephaly, four with macrocephaly, and five with growth retardation.

Twelve patients had neurological findings uncommon in ASD apart from microcephaly, including: oculomotor abnormalities (n = 4), sensorineural hearing deficit (n = 3), dysarthria (n = 3), ptosis (n = 2), movement disorders (n = 2), and hypertonia (n = 1). Five patients had seizures with one having medically refractory epilepsy.

Eight patients had markedly delayed early motor milestones. Of 14 patients with regression of previously acquired skills, nine had multiple regressions, six regressed at ages older than three years, and seven had regressions occurring with infections or other metabolic stresses. In six, gross motor skills were lost in addition to language skills. In one case, the timing of regression coincided with a recent vaccination.

Family history data were notable for likely autosomal recessive inheritance in one patient whose parents were first cousins. The family history suggested mitochondrial inheritance in three patients. Three other patients had mothers with features suggesting mitochondrial disease and four patients had sibs with either enzyme-defined mitochondrial disease and/or a clinical history consistent with mitochondrial disease.

Biochemical and Neuroimaging Data (Table 2; Tables S4 and S5)

Blood lactate was measured in all patients; 19 had at least one increased lactate level, 13 had multiple high levels and 14 had at least one lactate level greater than 3 mmol/L. Of 17 patients who had at least one blood pyruvate determination, nine (53% of those tested) had at least one increased pyruvate level. Plasma amino acids were analyzed for all patients; nine had at least one increased plasma alanine level and four had multiple high alanine levels.

Table 2. Biochemical and Neuroimaging Data.

	Number abnormal	Number tested	Percent of tested who were abnormal
Increased blood lactate level	19	25	76
Increased blood pyruvate level	9	17	53
Increased plasma alanine level	9	25	36
Increased serum AST and/or ALT level	13	25	52
Increased serum CK level	8	25	32
Abnormal urinary organic acid analysis	10	24	42
Increased fibroblast lactate: pyruvate ratio	3	15	20
Biochemical evidence of mitochondrial disease with any of the above tests	24	25	96
Abnormal cranial MRI	10	21	48
Increased lactate on cranial MRS	2	5	40

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The level of AST and/or ALT was increased in 13. One patient had an increased ALT with a normal AST and seven had elevated AST with normal ALT. Eight patients (28%) had increased serum CK levels. Ten patients (42% of those tested) had urinary organic acid abnormalities indicative of mitochondrial dysfunction. The fibroblast lactate/pyruvate ratio was increased for three patients.

Twenty-one patients underwent cranial MRI studies; five also had cranial MRS. Ten children had abnormalities on MRI (48% of those imaged), without a single finding predominating, while two patients had increased lactate on MRS (40% of those imaged).

Histological and Ultrastructural Findings (Table 3)

The most common histological abnormalities in muscle were atrophic or regenerating fibers (n = 8), reduced cytochrome oxidase (COX) staining (n = 6), variation in fiber size (n = 5), and increased myofiber lipid (n = 5). The most common ultrastructural abnormalities were abnormal mitochondrial morphology (n = 4) and increased number of mitochondria (n = 4).

Enzyme and Mitochondrial Mutation Data (Table 4; Table S6)

Twenty patients had deficient activity of a respiratory chain complex on tissue ETC or polarographic analysis; three others had phenotypes and biochemical profiles consistent with mitochondrial

Table 3. Muscle Histology and Ultrastructure.

	Number of patients
Moderate to large variation in fiber size	5
Atrophic or regenerating fibers	8
Focal inflammation	4
Increased myofiber lipid content	5
Type I fiber predominance	1
COX-negative fibers or reduced COX staining	6
Ragged red fibers	2
Increased number or subsarcolemmal aggregates of mitochondria	4
Mitochondria with abnormal morphology	4

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Table 4. Enzymology and Genetic Data.

	Number of patients	Percent of patients	Mutations
Complex I defect	16	64	
Complex II defect	2	8	
Complex III defect	5	20	
Complex IV defect	1	4	
mtDNA tRNA mutation	1	4	
mtDNA sequence variants of probable pathogenicity	2	8	3397A>G; 4295A>G
mtDNA sequence variants of unclear pathogenicity	4	16	3394T>C; 10394C>T; 11809T>C; 11984T>C

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disease and a sib with less than 20% activity on muscle ETC determination. Specific abnormalities included complex I defect in 16, complex III defect in five, complex II defect in two, and complex IV defect in one. Two patients had mtDNA mutations of likely pathogenicity and four had mtDNA sequence variants of unclear pathogenicity.

Discussion

The cohort of 25 patients reported here comprises the largest group of individuals with co-occurrence of ASD and defective oxidative phosphorylation reported to date. While previous case reports implicated an association of ASD and mitochondrial dysfunction, it could be argued that this was a chance occurrence in those individuals. Recent epidemiological studies indicate a population prevalence of ASD in about one in 166 children [2] and of mitochondrial disease in about one in 5–10,000 children [30,31]. These data, and the occurrence of definite oxidative phosphorylation dysfunction in approximately 7% of children with ASD in a population-based cohort [15], provide an epidemiological argument for a non-chance occurrence of ASD and mitochondrial disorders.

Our results indicate diverse and complex developmental, neurological, and medical phenotypes of persons with mitochondrial autism, nearly all of which differ from those of patients with idiopathic ASD. Although many children with ASD exhibit some degree of hypotonia, most attain their early gross motor milestones on time [32]. In contrast, 64% of our patients were delayed in attaining early developmental milestones and 32% were five or more standard deviations later than the mean in walking independently [33]. In addition, although regression has been reported to occur in approximately one third of autistic children, typically before age three years [34], 40% of our patients demonstrated unusual patterns of regression–either repeated regressions, regressions involving losses of gross motor function, and/or regressions after age three years.

Recently, there has been increased concern regarding a possible causative role of vaccinations in autistic children with an underlying mitochondrial cytopathy [35,36]. For one of our 25 patients, the child's autism/neurodevelopmental deterioration appeared to follow vaccination [12,36]. Although there may have been a temporal relationship of the events in this case, such timing does not prove causation. That said, there might be no difference between the inflammatory or catabolic stress of vaccinations and that of common childhood diseases, which are known precipitants of mitochondrial regression [37]. Large, population-based studies will be needed to identify a possible relationship of vaccination with autistic regression in persons with mitochondrial cytopathies.

In addition to atypical developmental patterns, non-neurological disorders were nearly universal in our patients. Although medical co-morbidities are not uncommon in individuals with ASD, they are not reported to be present with the high frequency noted here [38]. As in persons with idiopathic ASD, gastrointestinal dysfunction represented the most common non-neurological abnormality in our cohort. However, several of our patients had pancreatic dysfunction or liver disease–gastrointestinal disorders that are rare in persons with ASD [39,40]. The other organ system dysfunctions in our patients (cardiac, hematological, growth retardation, fatigability) are known manifestations of mitochondrial disease [41–43] but are not typical co-morbidities of primary autism [38].

Along with medical co-morbidities, an increased frequency of prenatal and perinatal complications has been reported in children with ASD [44]. However, whether these complications themselves increase the risk for autism or are consequences of an underlying disorder that predisposes to autism is unknown. Our study also shows a high frequency of prenatal/perinatal complications whose relationship to the children's autism is similarly unclear. Of note, an increased incidence of prenatal/perinatal complications has been reported for children with mitochondrial disease [45].

Besides prenatal complications, our data indicate a high frequency of multiple gestation births. The relevance of this finding is unclear but interesting in view of previous controversy about twinning as a risk factor for autism [46].

Also dramatically different from the general ASD population, the sex distribution of the subjects in our cohort is approximately 1:1. Primary ASD is 3–6 times more common in males than females and this ratio is even higher in PDD-NOS [1,2]. Since 56% of our patients have PDD-NOS, our finding of a nearly even distribution of males and females is especially notable.

From a biochemical perspective, patients' blood and urine laboratory data revealed marked interindividual variation that did not appear to correspond with specific ETC defects or clinical phenotypes. Significant intraindividual variation was also noted for determinations of blood lactate and pyruvate levels, plasma alanine levels, serum transaminases and CPK, and urinary organic acids, with intermittent normal levels in most cases. The histological and ultrastructural abnormalities noted on muscle biopsies were also varied amongst the subjects of this cohort and similar to results noted in other cohorts of children with mitochondrial electron transport chain disorders [47].

For most individuals with defects of oxidative phosphorylation, the diagnosis is made through ETC determination but an underlying nuclear or mitochondrial mutation usually cannot be identified [43,48,49]. The biochemical assessment of mitochondrial disorders, especially ETC enzyme assay, is complex and subject to limitations [49,50]. Even a clear-cut deficiency of one or more ETC activities *in vitro* does not prove a genetic defect of oxidative phosphorylation because ETC deficiencies can be secondary to other conditions [41,49–51]. The biochemical cut-off to diagnose a deficiency of an ETC varies by laboratory and multiple sets of diagnostic criteria are in use [49]. The criteria used in this study reflect an attempt to be diagnostically conservative. We excluded patients with clearly reduced but >20% ETC activity who lacked a pathogenic mutation even though less restrictive criteria are commonly used.

ETC complex I deficiency was the most prevalent enzyme defect, affecting 64% of our patients, followed by complex III deficiency, affecting 20%. It should be noted, however, that we cannot exclude the possibility that some patients might have biochemically mild forms of multiple ETC deficiencies. The predominance of ETC complex I deficiency is not unexpected and has been noted in cohorts of non-autistic patients with mitochondrial cytopathies [52]. This presumably reflects the large number of genes encoding complex I structure, assembly, and regulation.

Of patients who underwent mitochondrial genomic analysis, two had rare homoplasmic DNA sequence variants of likely pathogenicity: mtDNA 3397A>G and 4295A>C. mtDNA 3397A>G, which replaces methionine with valine in a highly conserved region of the ND1 subunit of complex I, has been implicated in various neurological phenotypes and other conditions [53–56]. Our interpretation of its likely pathogenicity is also based on the patient's reduced muscle ETC complex I activity and increased fibroblast lactate:pyruvate ratio. mtDNA 4295A>G occurs in an absolutely evolutionarily conserved sequence of mt $tRNA^{Ileu}$, reduces 3′ tRNAse processing efficiency [57], segregates with multiple disease states [58–60], and has been categorized as probably pathogenic [29]. A third patient had a rare sequence variant, 11984T>C. This mutation, reported previously in a child with Leigh syndrome, is likely pathogenic as it is a missense

mutation of the ND4 subunit of complex I that replaces a highly conserved tyrosine with histidine that, in turn, is predicted to markedly alter protein structure [61]. Its rarity and the absence of *in vitro* functional studies preclude assignment of probable pathogenicity at this time. For all three patients with these mutations there was intrafamilial phenotypic heterogeneity, as well as differences from phenotypes reported in the literature. Undetected heteroplasmy could explain these differences, but intrafamilial phenotypic variation with homoplasmic mitochondrial mutations has been reported and reasonable explanations proposed [42,62,63]. Because of the variability of phenotypes associated with these putative mutations, it is possible that there are important environmental or genetic factors in addition to the mtDNA mutation that contribute to the development of autism in a child with one of these mtDNA mutations. The mutations noted here are different from those described in prior case reports of children with autism and mitochondrial disease [10,13,14].

Overall, our results demonstrate substantial clinical heterogeneity of individuals with co-occurring autism and defects of mitochondrial oxidative phosphorylation, nearly all of whom we found to be clinically distinct from children with idiopathic autism. The data do not exclude the possibility of persons with isolated autism having a disorder of oxidative phosphorylation–in fact, one of our patients did not have any major clinical features that distinguished her from typical autism. In addition, it is possible, if not likely, that a still broader clinical, biochemical and genetic spectrum of mitochondrial autism exists.

Finally, data from multiple disciplines, especially research in developmental neurobiology and genetics, point to several underlying pathophysiological mechanisms in autism, including altered neurite morphology, synaptogenesis and cell migration due to abnormalities in distinct ensembles of proteins and pathways [64]. The data reported here, and other cases of mitochondrial autism, argue that defective mitochondrial oxidative phosphorylation is an additional pathogenetic basis for a subset of individuals with autism.

Supporting Information

Table S1 ASD Diagnosis and Mitochondrial Disease Criteria. PDD-NOS = Pervasive developmental disorder–not otherwise specified, MDC = mitochondrial disease criteria
Found at: doi:10.1371/journal.pone.0003815.s001 (0.07 MB DOC)

Table S2 Pertinent Medical History. GERD = gastroesophageal reflux disease, POTS = postural orthostatic tachycardia syndrome, RBBB = right bundle branch block, EF = ejection fraction, LVH = left ventricular hypertrophy
Found at: doi:10.1371/journal.pone.0003815.s002 (0.05 MB DOC)

Table S3 Regression History. Blank cells indicate an absence of regression of the type listed in the column
Found at: doi:10.1371/journal.pone.0003815.s003 (0.05 MB DOC)

Table S4 Biochemical Data. L:P = lactate to pyruvate ratio, DCA = dicarboxylic acids, EMA = ethylmalonate, 3-MG = 3-methylglutaconate * Value is listed only if level was higher than the upper limit of the reference interval † Patient had one high level but exact value is unknown
Found at: doi:10.1371/journal.pone.0003815.s004 (0.06 MB DOC)

Table S5 Neuroimaging. Blank cells indicate that patient did not undergo cranial MRI
Found at: doi:10.1371/journal.pone.0003815.s005 (0.04 MB DOC)

Table S6 Enzymology and mtDNA Testing 1 Testing performed at CIDEM Lab, Cleveland 2 Testing performed at Horizon Molecular Medicine LLC, Atlanta A: selected point mutations screened B: mtDNA sequencing C: whole mitochondrial genome scan by dHPLC P: mutation of probable pathogenicity U: mutation of unclear pathogenicity OXPHOS: polarographic determination of mitochondrial oxidative phosphorylation reactions * This patient does not have mitochondrial sequence changes indicative of haplogroup K †ETC complex III, when measured separately, was normal in these patients
Found at: doi:10.1371/journal.pone.0003815.s006 (0.06 MB DOC)

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Author Contributions

Conceived and designed the experiments: JRW RIK MB MRN. Analyzed the data: JRW RIK MB BHC KFM RLM RLK MRN. Wrote the paper: JRW RIK MB BHC KFM RLM RLK MRN. Obtained research funding: MRN.

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Vaccines and Autism

Autism Speaks statement on vaccinations

Over the last two decades, extensive research has asked whether there is any link between childhood vaccinations and autism. The results of this research are clear: Vaccines do not cause autism.

March 1, 2015

Over the last two decades extensive research has asked whether there is any link between childhood vaccines and autism. Scientific research has not directly connected autism to vaccines. Vaccines are very important. Parents must make the decision whether to vaccinate their children. Efforts must be continually made to educate parents about vaccine safety. If parents decide not to vaccinate they must be aware of the consequences in their community and their local schools.

Bob Wright Co-founder, Autism Speaks

Explore more: Science (/section/science), autism (/site-wide/autism), Autism Speaks (/site-wide/autism-speaks), Autism Spectrum (/site-wide/autism-spectrum), immunization (/site-wide/immunization), MMR (/site-wide/mmr), Vaccine (/site-wide/vaccine), vaccine safety (/site-wide/vaccine-safety), Vaccines (/site-wide/vaccines), Biology (/science/biology), Dissemination (/science/dissemination), Education (/family-services/education), Environmental Factors (/science/environmental-factors), Epidemiology/Prevalence (/science/epidemiologyprevalence), Policy Statements (/science/policy-statements-0)

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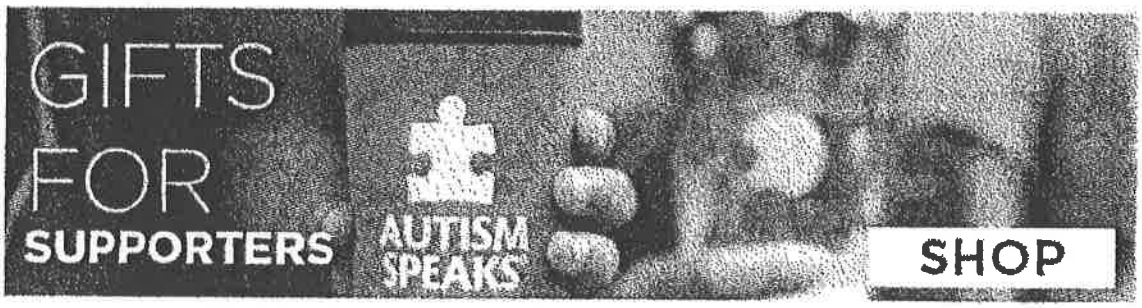

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(http://www.guidestar.org/organizations/20-2329938/autism-speaks.aspx)

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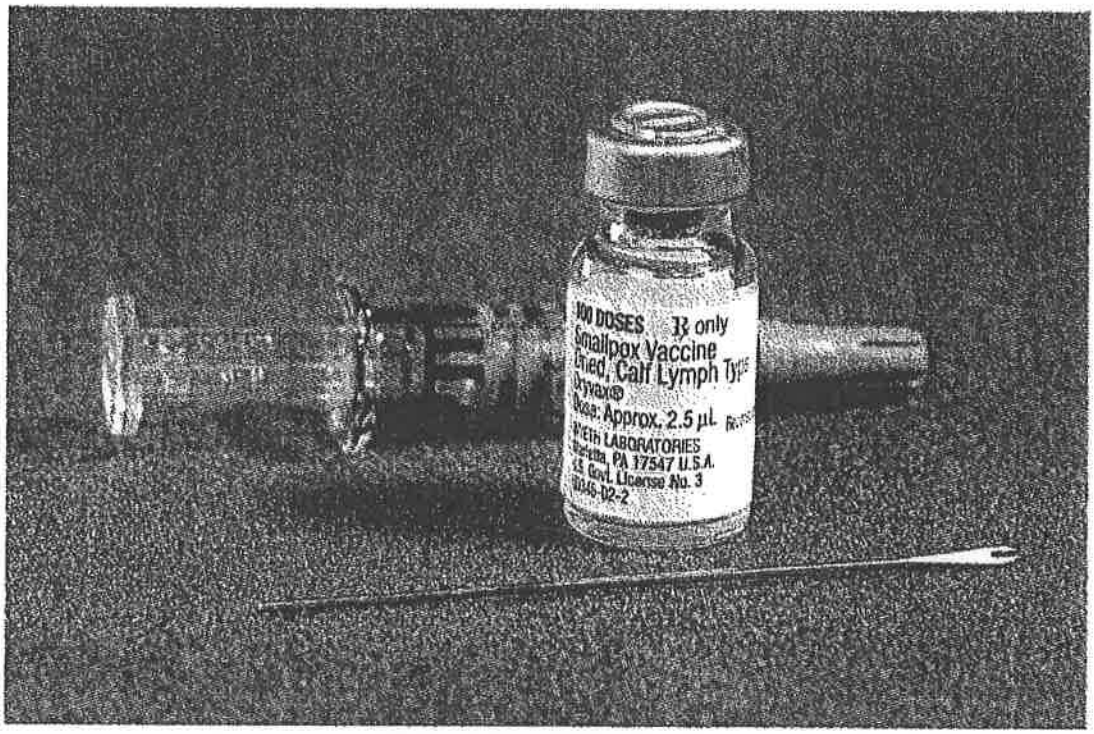
Debunking common myths about autism

By MANISH PARANJPE on March 31, 2016 · No Comment



James Gathany/Public Domain

There is no evidence to support the claim that vaccines cause autism.

Autism has long baffled scientists. Its intense heterogeneity and seemingly enigmatic cause have led clinicians and researchers to struggle to devise a cure. However, in the midst of this confusion, several problematic and often disturbing misconceptions about the nature of autism have arisen. I set out to dispel some of the myths surrounding autism.

Myth: Autism is a singular disease.
Fact: Autism, more accurately referred to as autism spectrum disorders (ASD), actually represents a set of heterogeneous diseases, including Fragile X Syndrome, Asperger's Syndrome, pervasive developmental disorder and classic autism. Of these subtypes, Fragile X Syndrome has been traced to a malfunction in a specific gene: FMR1. Unlike patients with other types of autism, patients with Asperger's Syndrome are said to have high-functioning autism due to their

seemingly normal cognitive abilities. It is exactly this vast heterogeneity in subtypes that makes ASD such a problematic disease to cure. To make inroads into autism research, scientists have often turned to simple genetic models of autism, such as Fragile X Syndrome. The jury is out, however, on whether the findings from these models can be applied to other forms of autism.

Myth: Early childhood vaccination can sometimes lead to autism.
Fact: This myth was circulated by a fraudulent 1998 article in Lancet in which British gastroenterologist Andrew Wakefield claimed to have found a link between autism and the measles, mumps and rubella (MMR) vaccine. The article has since been retracted, and Wakefield has been condemned by the scientific community for manipulating evidence. Yet the effects of Wakefield's article were widespread: Following his 1998 claim, vaccination rates in Ireland and England fell sharply, leading to an almost 20-fold increase in reported cases of measles from 1998 to 2007.
Many people still believe in this myth, but nothing could be further from the truth. We have a highly convincing body of evidence showing that there is no correlation between vaccinations and autism. A 2013 study conducted by the Centers for Disease Control (CDC) found no significant correlation between antibody stimulating proteins (such as those found in vaccines) and autism. A total of nine CDC-funded studies have shown that popular vaccine ingredients, such as mercury-based thimerosal, which were once thought to lead to autism, have been reported to have no correlation with autism.

Myth: People with autism are cold and unable to form meaningful social relationships.
Fact: Autism is a developmental disability characterized by not only abnormal brain structure, but also behavioral and cognitive problems. One of the most recognizable features of autism is social disconnection. Patients with autism may seem to show a lack of interest in interacting with external stimuli. For example, a 2005 study by Yale psychiatrist Fred Volkmar found that infants with autism are less responsive to human faces and voices compared to normal controls. However, autism is a spectrum of diseases, and many individuals with higher-functioning autism can successfully maintain social relationships. Furthermore, we must be careful not to confuse social disconnection with a cold affect. While individuals with autism may have trouble with social awareness and social interaction, they often exhibit a genuine affection for those around them.

Myth: Autism is caused solely by environmental factors.
Fact: Whole genome-wide association studies have been crucial in identifying certain risk genes for autism. A 2014 paper in Nature Genetics found that 49 percent of the risk for developing autism can be attributed to certain common risk genes. The subject of autism and one's genes remains the focus of research.

Myth: Indisviduals with autism have a low IQ.
Fact: Intellectual disorder sometimes presents as comorbid with autism. However, autism is a vast subset of disease and often individuals with autism, particularly Asperger's Syndrome, excel well beyond their peers in certain areas.

Autism is a set of complex neurological and developmental disorders of the brain. As the incidence of autism diagnosis becomes more prevalent in society, we must be increasingly careful to separate autism fact from myth.

FEATURE, slider

Debunking common myths about autism added by **MANISH PARANJPE** *on March 31, 2016*
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Johns Hopkins Bloomberg School of Public Health

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MMR/MEASLES VACCINE

- **A 32 year review of MMR vaccine finds it effective, safe and well-tolerated.** Llewelyn P et al. Vaccine 2012 (ahead of publication) link to PubMed *(9-6-12)*

- **New Vaccine Information Statement (VIS) for MMR.** The first VIS to include a barcode allowing scanning of selected information to a patient's record or immunization information system. *(4-20-12)* link

- **The Editors of The Lancet, a prominent medical journal, have retracted a controversial 1998 publication by Andrew Wakefield, et al:**
"Following the judgment of the UK General Medical Council's Fitness to Practice Panel on Jan 28, 2010, it has become clear that several elements of the 1998 paper by Wakefield et al are incorrect, contrary to the findings of an earlier investigation. In particular, the claims in the original paper that children were "consecutively referred" and that investigations were "approved" by the local ethics committee have been proven to be false. Therefore we fully retract this paper from the published record." GMC findings | Lancet retraction (may require password)
In 2004, 10 of the 12 original authors retracted the interpretation of the paper. (see below)

- **Rulings in cases testing MMR/thimerosal-autism link**
The assigned Special Masters of the United States Court of Federal Claims filed decisions on February 12, 2009 in the three test cases that allege MMR vaccines and thimerosal-containing vaccines can combine to cause autism. The three cases are Cedillo v. HHS, Hazlehurst v. HHS, and Snyder v. HHS. A table briefly describing the decisions as well as links to the entire text is available here. *(02/2009)*

- **Lack of Association between Measles Virus Vaccine and Autism with Enteropathy**
In a rigorous study, investigators from three institutions found no differences between children with autism and gastrointestinal disorders and control children who had gastrointestinal disorders, but not autism. There was no difference in the results of testing for measles vaccine virus in the intestine or with the timing of MMR and the onset of gastrointestinal disorders.

  These findings disprove the original hypothesis about measles vaccine and autism and refute an earlier study by one of the investigators. Parents should be confident in giving their children MMR as recommended by numerous experts and advisory groups.

  Horning M et al. "Lack of Association between Measles Virus Vaccine and Autism with Enteropathy: A Case-Control Study. PLoS ONE 2008;3 (9):E3140. link to article *(08/2008)*

- **A Canadian study reconfirms older findings ruling out an association between pervasive developmental disorder [PDD] (including autism) and high levels of ethylmercury exposures or MMR vaccines.**
The specific findings by Fombonne et al in Pediatrics include:
  * Autism and Thimerosal - thimerosal exposure was unrelated to the increasing trend in PDD prevalence
  * Autism and MMR - no association between MMR vaccinations (both 1 and 2 doses) and autism or PDD rates.

  The study found the highest rates of PDD in children with no thimerosal exposure (from vaccines). The study also noted a slight decrease in the rates of MMR vaccine at the same time as rates of PDD were increasing.

  Fombonne E et al. "Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations." Pediatrics 2006;118(1):139-50. [PubMed Abstract] *(07-2006)*

- **The US FDA has approved Merck's combination vaccine, ProQuad®** [Measles, Mumps, Rubella and Varicella (Oka/Merck) Virus Vaccine Live], for simultaneous vaccination against measles, mumps, rubella (German measles) and varicella (chickenpox) in children 12 months to 12 years of age. link *(09-08-05)*

- **MMR Vaccination and Pervasive Developmental Disorders: no association.**
Smeeth, et al report that MMR vaccination is not associated with an increased risk of pervasive developmental disorders (PDDs). The authors studied 1294 affected children and 4469 controls in the General Practioners Database in the United Kingdom and "We have found no convincing evidence that MMR vaccination increases the risk of autism or other PDDs". (09-15-04) PubMed Abstract Lancet

- **Institute of Medicine reports that MMR and thimerosal do not cause autism.**
The IOM committee concluded that the body of epidemiological evidence favors rejection of a causal relationship between the MMR vaccine and autism and between thimerosal-containing vaccines and autism. [link] May 17, 2004

- **Authors Retract Controversial Interpretation of 1998 Lancet Paper Linking MMR Vaccine to A New Syndrome of Bowel Disease and Autism.**
Statements from the authors and the Lancet editor. March 6, 2004

- **Investigations Reveal an Unreported Conflict of Interest and Problems With Reporting in Wakefield's 1998 Autism-MMR Study.**
Information on the investigation by The Lancet into problems with Andrew Wakefield's study. February 27, 2004.

- **Measles, Mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study.**
This paper by Taylor et al in the [Feb 16 2003] BMJ adds to the growing body of evidence that show no involvement of MMR vaccine in the development of autism. The authors report on their investigation of 473 and conclude that their data shows neither a "new variant' form of MMR-associated autism nor evidence of MMR contributing to the onset of autism. BMJ 2003;324:393-6. PubMed Abstract BMJ

- **MMR and autistic enterocolitis: consistent epidemiological failure to find an association.**
In News & Commentary in Molecular Psychiatry [Feb 2003], Fombonne and Cook review a recent paper by Taylor et al on MMR and Autistic Enterocolitis. Fombonne and Cook review Taylor's paper as well as the hypothesis by Wakefield et al that speculated about a connection between MMR and autism and ask, "How many more well-powered epidemiological investigations ... will be necessary for this hypothesis to be completely discarded". PubMed Link | Molecular Psychiatry 2003;8:133-4

- **A Population-based study of Measles, Mumps and Rubella Vaccination and Autism.**
A Danish study provides strong evidence against a causal relationship between MMR vaccination and autism. Madsen et al. NEJM 2002;347(19):1477-82. PubMed Abstract | NEJM

- **The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine.**
Barlow WE et al find no long-term adverse consequences from febrile seizures following administration of DTP and MMR vaccines. NEJM 2001;345(9):656-61. PubMed Abstract | NEJM

- **Measles-Mumps-Rubella Vaccine and Autistic Spectrum Disorder: Report From the New Challenges in Childhood Immunizations Conference Convened in Oak Brook, Illinois, June 12-13, 2000.** Pediatrics

2001;107(5). Halsey, Neal A.; Hyman, Susan L.
The writers of this report reviewed over 1,000 references in the medical literature and determined that the available research does not support the hypothesis that MMR vaccine causes autism, autism spectrum disorders or inflammatory bowel disease. A complete copy of this report is available in the online version of Pediatrics.
PubMed Abstract

- **Institute of Medicine (IOM) Committee Rejects Causal Relationship Between Measles-Mumps-Rubella Vaccine and Autism Spectrum Disorder**
At a public briefing on April 23, 2001 the Institute of Medicine's (IOM) Committee on Immunization Safety Review released a report in which they conclude that the evidence favors rejection of a causal relationship between the measles-mumps-rubella (MMR) vaccine and autism spectrum disorder, commonly known as autism. IOM Report

- **Evidence shows genetics, not MMR vaccine, determines autism** (AAP News December 1999) by Charles G. Prober, MD, FAAP.

- **No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study.** *(Lancet 1998;351:1327-8)* | PubMed Link
This Finnish study shows details of the 31 children who developed gastrointestinal symptoms after approximately three million were vaccinated. Dr. Peltola et al, after more than 10 years following adverse events associated with MMR vaccine, found no data showing an association between MMR vaccine and developmental disorders or inflammatory bowel disease.

- **No evidence to support an association between measles, measles vaccination and Crohn's disease.**
Three letters in June 6, 1998 British Medical Journal
- Second immunisation has not affected incidence in England. PubMed Link
- Crohn's disease has not increased in Finland. PubMed Link
- Age specific prevalences do not suggest association with in utero exposure. PubMed Link

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This page was last updated on June 09, 2016

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THIMEROSAL IN VACCINES

- **Latest rulings by US Court of Federal Claims on thimerosal-autism link**
  A table briefly describing the decisions as well as links to the entire text is available here. *(3/2010)*

- **A study of blood levels of mercury following receipt of thimerosal-containing vaccines in premature infants found that the blood half-life of intramuscular ethyl mercury is shorter than that of oral methyl mercury in adults.** Pichichero ME, et al. Mercury Levels in Premature and Low Birth Weight Newborn Infants after Receipt of Thimerosal-Containing Vaccines. J Pediatr 2009 [PubMed abstract]

- **Rulings in cases testing MMR/thimerosal-autism link**
  The assigned Special Masters of the United States Court of Federal Claims filed decisions on February 12, 2009 in the three test cases that allege MMR vaccines and thimerosal-containing vaccines can combine to cause autism. The three cases are Cedillo v. HHS, Hazlehurst v. HHS, and Snyder v. HHS. A table briefly describing the decisions as well as links to the entire text is available here. *(02/2009)*

- **Mercury's Removal Doesn't Stop Autism's Rise, Study Shows**
  Cases of the disorder continued to increase in California children from 2004 to 2007, even after a preservative was removed from vaccines. By Jia-Rui Chong, Los Angeles Times Staff Writer (01-08-08) link

- **Findings from a CDC-published followup study of thimerosal exposure and neurodevelopmental delay have been published in a NEJM article by Thompson et al.** [free link to full text] (09-

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27-07)

CDC has also posted a transcript of a Sep 26 2007 press briefing including Q&A following the briefing [link].

More than 1000 children with different thimerosal exposures from the prenatal period until 7 months of age were evaluated using a battery of 42 neurodevelopmental tests at 7-10 years of age. The analyses involved 378 comparisons of outcomes including possible differences of effects on boys vs. girls. Ninety-five percent of the analyses showed no differences in outcomes by thimerosal exposure. Five percent of the comparisons revealed differences in outcomes by thimerosal exposure. Using a cutoff of 5% for statistical significance, these findings would be expected by chance. More findings of slight improvement in scores with increasing thimerosal exposure were found than findings of decreased performance with increasing exposure. The effects in both directions on test performance were quite small. These findings have been interpreted as probable chance occurrences by the authors.

The study did find an increased rate of tic disorders associated with thimerosal. This finding had been observed in two prior studies and will be investigated further.

This study will undoubtedly undergo intense evaluation by many groups. CDC will be making the dataset available publicly so that other groups can conduct additional analyses.

- **A Canadian study reconfirms older findings ruling out an association between pervasive developmental disorder [PDD] (including autism) and high levels of ethylmercury exposures or MMR vaccines.**
The specific findings by Fombonne et al in Pediatrics include:
  - Autism and Thimerosal - thimerosal exposure was unrelated to the increasing trend in PDD prevalence.
  - Autism and MMR - no association between MMR vaccinations (both 1 and 2 doses) and autism or PDD rates.

The study found the highest rates of PDD in children with no thimerosal exposure

(from vaccines). The study also noted a slight decrease in the rates of MMR vaccine at the same time as rates of PDD were increasing.

Fombonne E et al. "Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations." Pediatrics 2006;118 (1);139-50. [pubmed abstract] (07-2006)

- **Table showing Thimerosal Content in Some US Licensed Vaccines** link - *updated October 2006.*

- **Burbacher et al. Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal.** Environmental Health Perspectives 2005;113. [abstract] [full article (pdf - 1047K)]. (04-21-05)

- **A new influenza vaccine will be available for the 2005/6 Flu Season** The FDA has approved the license supplement of sanofi pasteur (formerly Aventis Pasteur) to market a formula of their influenza vaccine produced without introducing preservatives at any step in the manufacturing process. Fluzone®, Influenza Virus Vaccine, No Preservative, Pediatric Dose is the only influenza vaccine approved for use in the U.S. in children as young as 6 months. The vaccine will be available in 0.25 mL pediatric dose and 0.50 mL for children 3 years and older. *(03-09-05)*

- **MMR Vaccination and Pervasive Developmental Disorders: no association.** Smeeth, et al report that MMR vaccination is not associated with an increased risk of pervasive developmental disorders (PDDs). The authors studied 1294 affected children and 4469 controls in the General Practioners Database in the United Kingdom and "We have found no convincing evidence that MMR vaccination increases the risk of autism or other PPDs". Lancet 2004;364(9438):963-9. (09-15-04)

- Institute of Medicine reports that MMR and thimerosal do not cause autism. The IOM committee concluded that the body of epidemiological evidence favors rejection of a causal relationship between the MMR

vaccine and autism and between thimerosal-containing vaccines and autism. *May 17, 2004*

- New Law Limits Actions Over Vaccine Preservative - an article in Harvard's *Focus* looks at vaccines and thimerosal, including commentary by IVS's Dr. Halsey on autism as well as the Homeland Security Bill. (01-10-03)

- Vaccines Do Not Cause Autism - Dr. Halsey clarifies his position after recent media attention: NYT Magazine, NPR radio programs Morning Edition and Diane Rehm Show (11-11/13-02)

- Report issued by the IOM's Immunization Safety Review Committee, Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders (10-01-01)

- Balancing Risks and Benefits: *Primum non nocere* Is Too Simplistic is Neal Halsey and Lynn Goldman's response to an earlier commentary regarding the delay of the birth dose of hepatitis B vaccine. They also include new information regarding methyl- and ethyl-mercury. (08-02-01)

- Information from the IOM meeting on Thimerosal-Containing Vaccines and Neurodevelopmental Outcomes, including a slide show presentation by IVS director, Dr. Halsey entitled "Commentary of Potential Risk from Thimerosal for Infants". (07-16-01)

- Information from the June 21, 2000 ACIP meeting regarding thimerosal: new vaccines without thimerosal, studies of mercury exposure in children and study of blood mercury level.

- New PHS/AAP statement and data on thimerosal in vaccines: June 22,2000.

- New Preservative-Free Hepatitis B Vaccine approved by FDA for pediatric and adolescent use (03-31-00).

- Limiting Infant Exposure to Thimerosal in Vaccines and Other Sources of Mercury *Neal Halsey's editorial on ways to cut down on infant exposure to mercury. (JAMA 1999;282(18):1763-5). (11-10-99)*

- CDC Announcement regarding a Thimerosal-free Hepatitis B Vaccine *On September 10, 1999, the CDC announced the availability of a thimerosal-free hepatitis B vaccine and recommended that routine hepatitis B vaccination policies for all infants be reintroduced immediately in hospitals where these policies had been discontinued.*

- Thimerosal in Vaccines — an Interim Report to Clinicians *The American Academy of Pediatrics has also recommended restoring routine neonatal immunization for infants born to HBsAg negative women when vaccines free of thimerosal preservative became available (Pediatrics September 1999;104:570-4).*

- New Thimerosal-free Hepatitis B Vaccine for Use in Infants *On August 27,1999, the FDA approved a modified hepatitis B vaccine (Recombivax HB) produced by Merck. The new product is distinguished from the original by an orange streak on the label stating "Preservative Free". Use of the new product should be limited to infants at this time in order to assure sufficient supplies for all children.*

- IVS Perspective on the Use of Thimerosal-Containing Vaccines *Slide Show presentation from August 11/12, 1999 Workshop on Thimerosal and Vaccines*

- Joint Statement of the American Academy of Pediatrics (AAP) and the U.S. Public Health Service (PHS) (7-7-99)

- Thimerosal, a Mercury-containing Preservative Used in Some Vaccines *Statement of the IVS position on mercury-containing vaccines. (7-8-99)*

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This page was last updated on **June 09, 2016**

Kennedy Krieger Institute

A comprehensive resource for children with disabilities

April 24, 2007

USDOJ/Civil Torts Branch/OCVL
1425 New York Ave. NW
Room 8119
Washington, D.C. 20005

RE: Cedillo case

At your request I have reviewed the medical records of Michelle Cedillo as well as the expert reports in this case, and have formulated the opinions below based on these materials, my knowledge and experience. My opinions are held to a reasonable degree of medical certainty.

By way of introduction, I am a pediatric neurologist with a special interest in behavioral neurology and autism. I have been practicing for 30 years since I completed my residency training in 1977, in two academic settings for 22 years and private practice for 11 years. During practice in Knoxville, TN, I became interested in autism in the mid-eighties and have concentrated my efforts in this field since returning to Baltimore in 1994, at Kennedy Krieger Institute and Johns Hopkins University, in clinical practice, research and teaching. Over the past 21 years, I have evaluated and followed approximately 4,000 children and adults with autism. My major research interest has been the role of the immune system in autism, and I have published on this and related areas in autism research, as indicated in my curriculum vitae. My interests and collaborations have led to new approaches to the understanding of immunity in families with autism, the role of immune system genes, immune factors in cerebrospinal fluid, and immune activation in the brain in autism, among others. I also have experience in drug studies and am a member of the Drug Therapy Committee and a grant reviewer for Cure Autism Now and Autism Speaks. I was an organizer of the first Autism and Immune System Workshop

held recently in Pasadena, and I am currently editing a book with 20 authors, entitled *Autism: Current Theories and Evidence.*

The case of Michelle Cedillo presents complex questions due to the unusual nature of her findings and clinical course, as well as the etiologies (causes) for autism alleged by the petitioners' experts. Autism itself is a heterogeneous group of neurodevelopmental disorders that present with similar clinical signs, and are diagnosed by observed language, social and behavioral characteristics. About 10% of affected children can have any of a large number of "known," diagnosable conditions by examination and using currently available laboratory tests -- conditions such as fragile X syndrome, Rett syndrome and tuberous sclerosis.[1] The designation of a child as "autistic" is therefore no more specific than saying a patient is "hypertensive" or has "pneumonia," since these conditions require the physician to investigate the underlying causes in order to provide specific treatment. The other 90% of children with autism remain "idiopathic," meaning we still do not know the medical basis for their symptoms (i.e., their causes have not been established based on current scientific evidence). Approximately 30% of children with autism present with signs of regression or loss of previously acquired language and social skills, typically between 16 and 24 months of age, although studies have shown that despite the appearance of prior "normality," most had subtle signs of abnormal development during the first year of life. Gastrointestinal symptoms are associated in about 24%,[2] and epilepsy in up to 40% of children with autism, both of which usually improve over time.

In the immune system, a variety of atypical findings have been reported in children with autism, as measured in the blood.[3] These have been difficult to characterize, because of variability among findings in different studies, most of which cannot be compared due to small numbers of patients and their different techniques and measurements. In spite of these findings, severe immune deficiencies typically do not occur in autism, and there is no evidence that correction of mild immune deficiency states (e.g., with administration of immunoglobulins) provides benefit for autistic symptoms.[4] There is also no evidence for correlations or causal connections between findings in the "systemic" immune system (in

the blood and lymph glands) and immune or other findings in the brain in autism Although antibodies to a variety of brain antigens have been described in the blood from children with autism, they have also been found in normal "control" children and have not been proven to play a role in causing or contributing to autism.[5] Indeed, a current focus of immune research is on the *mother's* immune system, which shows that maternal antibodies directed to the developing human fetal brain may be pathogenic (cause pathology) before birth.[6] The effects of these human maternal antibodies have been demonstrated following placental transfer in animal models, producing abnormal behaviors and changes in the brain of the offspring.[7] This implies that differences in the immune system in autism are likely to be important before birth, acting between the mother and fetus. My colleagues and I have also described signs of immune activation in both the cerebrospinal fluid (CSF) of living children, and in postmortem brain tissue from children and adults with autism.[8] There is no evidence in brain tissue or CSF of infection,[9] and the immune activation we observed contained pro-inflammatory as well as anti-inflammatory elements.[8] Further research is needed to determine if the immune activation in the brain in autism is harmful or beneficial to the brain (it may be either or both), is a residual immature pattern of development from an earlier age, or results from abnormal regulation of brain cells (neurons or astroglia) or a genetic abnormality affecting the immune system, among other possibilities.

Autism is primarily a genetically determined disorder.[10] There is a hypothetical basis, but very limited evidence, for environmental factors (such as stress or the drug terbutaline[11]) that may act together with an individual's genetic susceptibility to increase the risk of autism. There is strong evidence that the origins of autism begin before birth, based on genetic and anatomical studies as well as chemical findings at birth in children who go on to develop autism.[12,13] The usual time period when autism appears and is diagnosed during the 2nd and 3rd years of life reflects the dynamic nature of the child's developing brain and the appearance of pre-programmed disordered expression of genes and pre-existing cellular abnormalities that result in the child's regression with loss of language and social skills. The best example of such developmental regression occurs in Rett syndrome, a genetic disorder that was otherwise undifferentiated from autistic disorder

until the genetic abnormality was discovered in 1999; it is now considered a well-defined cause of autism, the boundaries of which are continuing to expand as more genetic variants are being discovered.[14]

Based on this background, my opinions in this case cover six areas:

1. There is no scientific basis for a connection between measles, mumps and rubella (MMR) vaccine or mercury (Hg) intoxication and autism. Despite well-intentioned and thoughtful hypotheses and widespread beliefs about apparent connections with autism and regression, there is no sound evidence to support a causative relationship with exposure to both, or either, MMR and/or Hg. Michelle Cedillo had a thorough and normal immunology evaluation by Dr. Sudhir Gupta, showing no signs of immunodeficiency that would have precluded her from receiving or responding normally to MMR vaccine.

2. Michelle Cedillo's developmental regression was likely to have been pre-programmed before birth to emerge, as it does in Rett syndrome, long after birth. Although in rare instances MMR can be associated with an acute encephalopathy, this event did not occur here. While parental description of the emergence of Michelle Cedillo's condition has been inconsistent, no description coincides with an acute encephalopathic insult. Petitioners' experts postulate a chronic brain injury. Again, there is no scientific basis for attributing autism to MMR administration.

3. The pediatric growth records show abnormal growth in height, weight and head circumference during Michelle's first 18 months of life. At birth, her weight was at the 50th, while length was at the 90th percentile. By 6 months of age, all measurements were well above the normal growth curve for age. However, at 11 years her height was at the 75th percentile, although she continued to be overweight. This unusual growth pattern suggests a genetic disorder of growth, a so-called "overgrowth syndrome," such as Sotos syndrome[15], which has been

associated with autism. Although she was said to have had extensive genetic testing, I was unable to locate results of such testing in the records, nor was there a genetic consultation recorded, as recommended by Dr. B. J. Freeman (in 7/00), among others. Rapid acceleration of head growth has been documented during early postnatal development in autism (but not height or weight), the causes for which are still unknown.

4. Although Michelle's early developmental milestones were later said to be normal, they were not. Dr. Karlsson Roth recorded during an early diagnostic evaluation that Michelle did not smile until 4-6 months, roll front to back until 4-5 months, crawl until 9 months, sit until 11 months or walk until 16 months. Such delays suggest subtle abnormalities of development during the first year of life, preceding the administration of MMR vaccine.

5. Associated medical disorders in children with autism may occur commonly or uncommonly, but are not diagnostic of autism, nor do they indicate or imply the etiology of autism. For example, gastroesophageal reflux and lymphoid hyperplasia in the gastrointestinal tract, and epilepsy in the nervous system, both occur together with autism, however neither is diagnostic or definitive with respect to its causes or treatment. The medical treatment of these and other associated medical disorders can alleviate suffering and help a child respond better to autism therapies (such as speech and occupational therapy), but in neither case do the treatments change the underlying autism. Crohn's disease, uveitis and arthritis, conditions attributed to Michelle, have no correlation with autism.

6. Autism, in most cases, begins before birth, and the maternal "environment" in the womb is likely to be important in the process. A number of factors are likely to increase susceptibility to autism, such as autoimmune disorders in the mother, including allergy and asthma (for which Theresa Cedillo was treated and followed). Autoimmune disorders are more common in the mothers and families

with autism than the general population, however such associations have not been found in the children.[16, 17]

In summary, the factors outlined above strongly suggest that Michelle Cedillo had unusual signs and symptoms leading up to the appearance of developmental regression and the recognition of autism. Her medical course has also been unusual and complex but does not imply a relationship to a specific etiology. Furthermore, there is no evidence of an association between autism and the alleged reaction to MMR and Hg, and it is more likely than not, that there is a genetic basis for autism in this child.

Sincerely,

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